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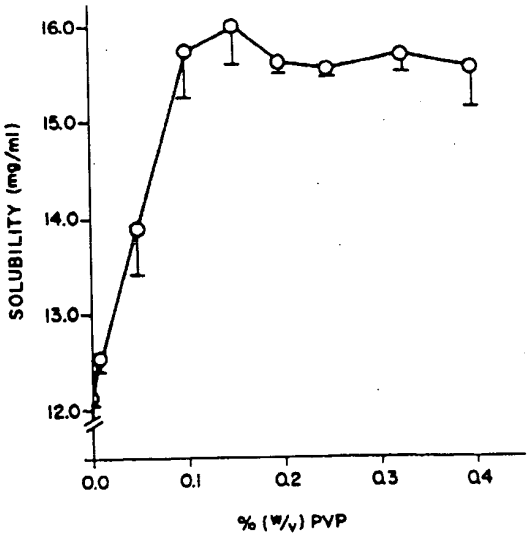
(54) Cyclodextrin complexation.

(57) The invention provides a method for enhancing the complexation of a cyclodextrin with a lipophilic and/or water-labile drug, comprising combining from about 0.1 to about 70% (weight/volume) of a cyclodextrin and from about 0.001 to about 5% (weight/volume) of a pharmaceutically acceptable, pharmacologically inactive, water-soluble polymer in an aqueous medium, the polymer and cyclodextrin being dissolved in the aqueous medium before the drug is added, the aqueous medium which comprises the polymer and cyclodextrin being maintained at from about 30 to about 150°C for a period of from about 0.1 to about 100 hours before, during and/or after the drug is added, optionally followed by removal of water. Related methods, co-complexes of drug/cyclodextrin/polymer, pharmaceutical compositions and cyclodextrin/polymer complexing agents are also provided. Analogous methods, co-complexes and compositions in which the drug is replaced with a food additive, cosmetic additive or agrochemical are also described.

Fig.1



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Field of the Invention

The present invention relates to the use of certain polymers in the preparation of cyclodextrin-drug complexes as a means for increasing the solubilizing and stabilizing effects of cyclodextrin derivatives on drugs, and complexation therewith. Pharmaceutical compositions comprising complexes prepared according to these methods are characterized by fast and efficient drug release. The invention further relates to polymer/cyclodextrin complexing agents. Still further, the invention relates to use of the polymers to increase the solubilizing and stabilizing effects of cyclodextrins on food additives, agrochemicals and chemicals used in cosmetics, and complexation therewith.

Background of the Invention

Formulation of pharmaceutical dosage forms is frequently hampered by the poor aqueous solubility and stability of the drugs, which in turn can severely limit their therapeutic application. Also, the slow dissolution of solid state drug formulations and the side-effects of some drugs result from their poor aqueous solubility. Drug degradation products, formed in the pharmaceutical dosage forms, can also result in severe side-effects. Increasing drug solubility and stability through appropriate formulation can, thus, lead to increased therapeutic efficiency of the drug. Various methods have been used to increase the solubility and stability of drugs, such as the use of organic solvents, emulsions, liposomes and micelles, adjustments of pH and the dielectric constant of the solvent system, chemical modifications, and complexation of the drugs with appropriate complexing agents, e.g. cyclodextrins. Similar approaches have been taken to increase the solubility and stability of food additives, agrochemicals and cosmetic additives.

Cyclodextrins were first isolated by Villiers in 1891 as a digest of *Bacillus amylobacter* on potato starch [see A. Villiers: Sur la fermentation de la fécule par l'action du ferment butyriqué. *C.R. Acad. Sci.*, **112**, 536-538 (1891)], but the foundations of cyclodextrin chemistry were laid down by Schardinger in the period 1903-1911 [see, for example, F. Schardinger: Uber thermophile Bacterien aus verschiedenen Speisen und Milch, sowie über einige Umsetzungsproducte darselben in kohlenhydrathaltigen Nährlösungen, darunter krystallisierte Polysaccharide (Dextrine) aus Stärke, Z. *Unters. Nahr. Genußm.*, **6**, 865-880 (1903)] and much of the older literature refers to cyclodextrins as Schardinger's dextrins. Until 1970, only small amounts of cyclodextrins could be produced in the laboratory and the high production cost prevented the usage of cyclodextrins in industry. In recent years, dramatic improvements in cyclodextrin production and purification have been achieved and the cyclodextrins have become much cheaper. This has made industrial application of cyclodextrins possible.

Cyclodextrins are cyclic oligosaccharides with hydroxyl groups on the outer surface and a void cavity in the center. Their outer surface is hydrophilic, and therefore they are usually soluble in water, but the cavity has a lipophilic character. The most common cyclodextrins are α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin, consisting of 6, 7 and 8 α-1,4-linked glucose units, respectively. The number of these units determines the size of the cavity.

Cyclodextrins are capable of forming inclusion complexes with a wide variety of hydrophobic molecules by taking up a whole molecule, or some part of it, into the cavity. The stability of the complex formed depends on how well the guest molecule fits into the cyclodextrin cavity. Common cyclodextrin derivatives are formed by alkylation (e.g. methyl- and ethyl-β-cyclodextrin) or hydroxyalkylation of the hydroxyl groups (e.g. hydroxypropyl- and hydroxyethyl-derivatives of α-, β-, and γ-cyclodextrin) or by substituting the primary hydroxyl groups with saccharides (e.g. glucosyl- and maltosyl-β-cyclodextrin). Hydroxypropyl-β-cyclodextrin and its preparation by propylene oxide addition to β-cyclodextrin, and hydroxyethyl-β-cyclodextrin and its preparation by ethylene oxide addition to β-cyclodextrin, were described in a patent of Gramera *et al.* (United States Patent No. 3,459,731, issued August 1969) over 20 years ago. For a comprehensive review of cyclodextrins see *Cyclodextrins and their industrial uses*, editor Dominique Duchêne, Editions de Santé, Paris, 1987. For a more recent overview, see J. Szejtli: Cyclodextrins in drug formulations: Part I, *Pharm. Techn. Int.* 3(2), 15-22 (1991); and J. Szejtli: Cyclodextrins in drug formulations: Part II, *Pharm. Techn. Int.* 3*(3)*, 16-24 (1991).

Numerous reports have been published with respect to the solubilizing effects of cyclodextrins. The general procedure described in these reports for preparing aqueous cyclodextrin solutions containing various drugs is as follows: An excess amount of the drug is added to an aqueous cyclodextrin solution and the suspension formed is agitated for up to one week at room temperature. Then the suspension is filtered or centrifuged to form a clear drug-cyclodextrin complex solution. For the preparation of solid formulations of the drug-cyclodextrin complex, the water is removed from the aqueous drug-cyclodextrin complex solution by evaporation in a rotation evaporator, in a spray dryer or by lyophilization. Pitha (Josef Pitha: Administration of sex hormones in the form of hydrophilic cyclodextrin derivatives, United States Patent No. 4,596,795, issued June

24, 1986) describes inclusion complexes of sex hormones, particularly testosterone, progesterone, and estradiol, with specific cyclodextrins, preferably hydroxypropyl-β-cyclodextrin and poly-β-cyclodextrin. The complexes enable the sex hormones to be successfully delivered to the systemic circulation via the sublingual or buccal route. In another patent (Josef Pitha: Pharmaceutical preparations containing cyclodextrin derivatives, United States Patent No. 4,727,064, issued February 23, 1988) Pitha describes formulations of a number of drugs with various cyclodextrin derivatives, mainly hydroxypropyl-β-cyclodextrin but also hydroxypropyl-γ-cyclodextrin. In a series of patents (N.S. Bodor: Improvements in redox systems for brain-targeted drug delivery, United States Patent No. 5,002,935, issued March 26, 1991; N.S. Bodor: Pharmaceutical formulations for parenteral use, United States Patent No. 4,983,586, issued January 8, 1991; N.S. Bodor: Redox systems for brain-targeted drug delivery, United States Patent No. 5,017,566, issued May 21, 1991; and N.S. Bodor: Pharmaceutical formulations for parenteral use, United States Patent No. 5,024,998, issued June 18, 1991), Bodor describes formulations of a number of drugs with hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of β- and γ-cyclodextrin. Also, Brauns and Müller (U. Brauns and B.W.W. Müller: Pharmazeutische Präparate von in Wasser schwerlöslichen oder instabilen Arznelstoffen und Verfahren zu Ihrer Herstellung, European Patent No.: 0 149 197 B1 dated March 21, 1990) have described formulations of drugs with various β-cyclodextrin derivatives, mainly hydroxypropyl-β-cyclodextrin. The solubilizing and stabilizing effects of hydroxypropyl-β-cyclodextrin on drugs have been reviewed by T. Loftsson, M.E. Brewster, H. Derendorf and N. Bodor: 2-Hydroxypropyl-β-cyclodextrin: Properties and usage in pharmaceutical formulations. *Pharm. Ztg. Wiss.* 4/136: 5-10 (1991).

Methods of preparing drug-cyclodextrin complexes have been described by Hirayama and Uekama [F. Hirayama and K. Uekama: Methods of investigating and preparing inclusion compounds. In: D. Duchêne (editor), Cyclodextrins and their industrial uses. Editions de Santé, Paris, 1987, pp. 133-172]. In solution, the drug-cyclodextrin complexes are prepared by the simple method described above and the complexation evaluated by determination of stability constants by a solubility method, a kinetic method, a spectroscopic method or some other analytical method. On a laboratory scale, solid drug-cyclodextrin complexes are usually formed by lyophilization of drug-cyclodextrin complex solution, but on an industrial scale, other methods are also used such as the kneading method, spray-drying, coprecipitation, neutralization and grinding methods. In none of these methods are water-soluble pharmaceutical polymers, or other polymers in general, used for enhancing the drug-cyclodextrin complexation.

There are few samples of formation of drug-cyclodextrin complexes by heating. Thus, Hassan *et al., Int. J. Pharm.* **58**, 19-24 (1990), prepared a famotidine-β-cyclodextrin complex by adding the drug to aqueous β-cyclodextrin solution, heating the mixture under reflux for 1 hour and then stirring it at room temperature for 5 days. The solution which formed was concentrated by evaporation under vacuum and the precipitate which formed was filtered and dried under vacuum at 50°C. In a series of articles, Nakai *et al.* describe how they make cyclodextrin inclusion complexes by heating ground mixtures of physical mixtures to 60 to 130°C in sealed containers. See Nakai *et al., Chem. Pharm. Bull.* **35**(11),4609-4615 (1987); Nakai *et al., Chem. Pharm. Bull.* 37(4), 1055-1058 (1989); Nakai *et al., Chem. Pharm. Bull.* **38**(3), 728-732 (1990); Nakai *et al., Chem. Pharm. Bull.* **38**(5), 1345-1348 (1990); and Nakai *et al., Chem. Pharm. Bull.* **39**(6), 1532-1535 (1991). Finally, Schmidt and Maier [E.Schmidt and H.G. Maier: Thermostabile Bindung von Aromastoffen an Starke. Teil 2: Bindung von Menthol durch Autoklavieren, *Starch/Stärke,* **39**(6), 203-207 (1987)] describe formation of thermostable binding of menthol to various types of starches, including β-cyclodextrin, by autoclaving. In none of the above mentioned articles are starches, or other polymers, used to enhance complexation of drugs by cyclodextrins.

Due to the negative enthalpy of cyclodextrin complexation, the solubility enhancement of drugs by aqueous cyclodextrin solutions is generally larger at low temperature than at high temperature [T. Loftsson and N. Bodor: Effects of 2-hydroxypropyl-β-cyclodextrin on the aqueous solubility of drugs and transdermal delivery of 17β-estradiol, *Acta Pharm. Nord.*, **1**(4), 185-193 (1989)]. Also, additives such as sodium chloride, buffer salts, surfactants and organic solvents (e.g. ethanol) usually reduce the solubilizing effects of cyclodextrins.

Summary and Objects of the Invention

One object of the present invention is to provide a method for enhancing the complexation of cyclodextrins with lipophilic and/or water-labile drugs, food additives, cosmetic additives and agrochemicals.

Another object of the invention is to provide a method for increasing the solubilizing and stabilizing effects of cyclodextrins on drugs which are insoluble or sparingly soluble or unstable in water, and on food additives, cosmetic additives and agrochemicals which are insoluble or sparingly soluble or unstable in water.

Another object of the invention is to provide novel co-complexes of drugs, cyclodextrins and selected polymers, and of food additives, cosmetic additives and agrochemicals, with cyclodextrins and selected polymers.

Yet another object of the invention is to provide pharmaceutical compositions comprising novel drug com-

plexes, as well as analogous food, cosmetic and agricultural compositions.

Still another object of the invention is to provide a novel complexing agent for use in solubilizing and/or stabilizing a lipophilic and/or water-labile drug, food additive, cosmetic additive or agrochemical.

In accord with these and other objects, the present invention provides the following:

(1) A method for enhancing the complexation of a cyclodextrin with a lipophilic and/or water-labile drug, comprising combining from about 0.1 to about 70% (weight/volume) of cyclodextrin and from about 0.001 to about 5% (weight/volume), preferably from about 0.01 to about 0.5% (weight/volume), of a pharmaceutically acceptable, pharmacologically inactive, water-soluble polymer with a lipophilic and/or water-labile drug in an aqueous medium to form a drug complex, the polymer and cyclodextrin being dissolved in the aqueous medium before the drug is added, and the aqueous medium being maintained at from about 30 to about 150°C for a period of from about 0.1 to about 100 hours before, during and/or after the drug is added, optionally followed by removal of water;

(2) A method for solubilizing and/or stabilizing a lipophilic and/or water-labile drug in an aqueous medium, comprising complexing the drug in an aqueous medium with from about 0.1 to about 70% (weight/volume) of cyclodextrin and from about 0.001 to about 5% (weight/volume), preferably from about 0.01 to about 0.5% (weight/volume), of a pharmaceutically acceptable, pharmacologically inactive, water-soluble polymer, the polymer and cyclodextrin being dissolved in the aqueous medium before the drug is added, and the aqueous medium being maintained at from about 30 to about 150°C for a period of from about 0.1 to about 100 hours before, during and/or after the drug is added;

(3) A co-complex of a lipophilic and/or water-labile drug with a cyclodextrin and a pharmaceutically acceptable, pharmacologically inactive, water-soluble polymer, the ratio by weight of cyclodextrin to polymer being from about 4:1 to about 50,000:1, preferably from about 100:1 to about 10,000:1;

(4) A pharmaceutical composition comprising:

(a) a drug complex prepared by complexing, in an aqueous medium, a lipophilic and/or water-labile drug with from about 0.1 to about 70% (weight/volume) of cyclodextrin in the presence of from about 0.001 to about 5% (weight/volume), preferably from about 0.01 to about 0.5% weight/volume, of a pharmaceutically acceptable, pharmacologically inactive, water-soluble polymer, the polymer and cyclodextrin being dissolved in the aqueous medium before the drug is added, and the aqueous medium being maintained at from about 30 to about 150°C for a period of from about 0.1 to about 100 hours before, during and/or after the drug is added, optionally followed by removal of water; and

(b) a non-toxic, pharmaceutically acceptable carrier therefor;

(5) A pharmaceutical composition comprising:

(a) a co-complex of a lipophilic and/or water-labile drug with a cyclodextrin and a pharmaceutically acceptable, pharmacologically inactive, water-soluble polymer, the ratio by weight of cyclodextrin to polymer being from about 4:1 to about 50,000:1; preferably from about 100:1 to about 10,000:1; and

(b) a non-toxic, pharmaceutically acceptable carrier therefor; and

(6) A complexing agent for use in solubilizing and/or stabilizing a lipophilic and/or water-labile drug, comprising a cyclodextrin and a pharmaceutically acceptable, pharmacologically inactive, water-soluble polymer, the ratio by weight of cyclodextrin to polymer being from about 4:1 to about 50,000:1, preferably from about 100:1 to about 10,000:1, said complexing agent being formed by heating the cyclodextrin and polymer in an aqueous medium at from about 30 to about 150°C for a period of from about 0.1 to about 100 hours.

The present invention further provides methods and compositions analogous to those listed above, in which the lipophilic and/or water-soluble drug is replaced by a lipophilic and/or water-soluble food additive, cosmetic additive or agrochemical.

Brief Description of the Drawings

Other objects and advantages of the present invention will be apparent from the following detailed description and accompanying drawings, in which:

Fig. 1 is a plot of the solubilization of hydrocortisone, in mg/ml, in aqueous 10% HPβCD (2-hydroxypropyl-β-cyclodextrin) MS 0.6 solution containing varying amounts of PVP (polyvinylpyrrolidone);

Fig. 2 is a series of plots depicting the dissolution profile of hydrocortisone from tablets containing hydrocortisone-HPβCD complex: Δ, 0% (w/v) CMC; ♦, 0.1% (w/v) CMC; o, 0.25% (w/v) CMC; and

Fig. 3 is a pair of plots illustrating the effect of 1% (w/v) acetazolamide eye drop solution on the intraocular pressure (IOP) of normotensive, conscious, albino rabbits, wherein the right eye received the drug (O) and the left eye was the control (□).

Detailed Description of the Invention and Preferred Embodiments

Here and throughout this description, the following definitions are applicable:

The term "lipophilic" is used herein to describe drugs (or food additives or cosmetic additives or agrochemicals) which are lipid-soluble and hydrophobic, i.e. which are insoluble or sparingly soluble in water.

The term "water-labile" is used herein to describe drugs (or food additives or cosmetic additives or agrochemicals) which are unstable in water.

Cyclodextrins for use in the present invention include the natural cyclodextrins and their derivatives, including the alkylated and hydroxyalkylated derivatives and the branched cyclodextrins. Cyclodextrins and their derivatives which have been previously described as useful for complexation with drugs are of particular interest herein. In addition to α-, β- and γ-cyclodextrins, the ether and mixed ether derivatives and those derivatives bearing sugar residues are of special interest. Especially useful herein are the hydroxyethyl, hydroxypropyl (including 2- and 3-hydroxypropyl) and dihydroxypropyl ethers, their corresponding mixed ethers and further mixed ethers with methyl or ethyl groups, such as methylhydroxyethyl, ethyl-hydroxyethyl and ethylhydroxypropyl ethers of α-,β- and γ-cyclodextrin; and the maltosyl, glucosyl and maltotriosyl derivatives of α, β- and γ-cyclodextrin, which may contain one or more sugar residues, e.g. glucosyl or diglucosyl, maltosyl or dimaltosyl, as well as various mixtures thereof, e.g. a mixture of maltosyl and dimaltosyl derivatives. Specific cyclodextrin derivatives for use herein include hydroxypropyl-β-cyclodextrin, hydroxyethyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, hydroxyethyl-γ-cyclodextrin, dihydroxypropyl-β-cyclodextrin , glucosyl-α-cyclodextrin, glucosyl-β-cyclodextrin, diglucosyl-β-cyclodextrin, maltosyl-α-cyclodextrin, maltosyl-β-cyclodextrin , maltosyl-γ-cyclodextrin, maltotriosyl-β-cyclodextrin, maltotriosyl-γ-cyclodextrin and dimaltosyl-β-cyclodextrin , and mixtures thereof such as maltosyl-β-cyclodextrin/dimaltosyl-β-cyclodextrin, as well as methyl-β-cyclodextrin. Procedures for preparing such cyclodextrin derivatives are well-known, for example, from Bodor United States Patent No. 5,024,998 dated June 18, 1991, and references cited therein. Particularly preferred cyclodextrins for use in the present invention are hydroxypropyl, hydroxyethyl, dihydroxypropyl, glucosyl and maltosyl derivatives of α-, β- and γ-cyclodextrin, and their mixtures, especially those having a molar degree of substitution of from about 0.05 to about 10. The expression "molar degree of substitution" is used in the same sense as employed in Brauns and Müller European Patent No. 0149197 B1.

Suitable polymers for use herein are those which are soluble in water, are acceptable for use in pharmaceuticals and are pharmacologically inactive. Such polymers are well-known excipients commonly used in the field of pharmaceutical formulations. [See, for example, *Remington's Pharmaceutical Sciences,* 18th edition, Alfonso R. Gennaro (editor), Mack Publishing Company, Easton, PA, 1990, pp. 291-294; Alfred Martin, James Swarbrick and Arthur Commarata, *Physical Pharmacy. Physical Chemical Principles in Pharmaceutical Sciences,* 3rd edition, Lea & Febinger, Philadelphia, PA, 1983, pp. 592-638; A.T. Florence and D. Altwood, Physicochemical Principles of Pharmacy, 2nd edition, MacMillan Press, London, 1988, pp. 281-334.] Suitable polymers include water-soluble natural polymers, water-soluble semi-synthetic polymers (such as the water-soluble derivatives of cellulose) and water-soluble synthetic polymers. The natural polymers include polysaccharides such as inulin, pectins, algin derivatives (e.g. sodium alginate) and agar, and polypeptides such as casein and gelatin. The semi-synthetic polymers include cellulose derivatives such as methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, their mixed ethers such as hydroxypropyl methylcellulose and other mixed ethers such as hydroxyethyl ethylcellulose and hydroxypropyl ethylcellulose, hydroxypropyl methylcellulose phthalate and carboxymethylcellulose and its salts, especially sodium carboxymethylcellulose. The synthetic polymers include polyoxyethylene derivatives (polyethylene glycols) and polyvinyl derivatives (polyvinyl alcohol, polyvinylpyrrolidone and polystyrene sulfonate) and various copolymers of acrylic acid (e.g. carbomer). Other natural, semi-synthetic and synthetic polymers not named here which meet the criteria of water solubility, pharmaceutical acceptability and pharmacological inactivity are likewise considered to be within the ambit of the present invention. Particularly preferred polymers for use herein are sodium carboxymethylcellulose, hydroxypropyl methylcellulose and polyvinylpyrrolidone.

Water-soluble polymers for use with drugs herein, as pointed out above, need to be pharmaceutically acceptable and pharmacologically inactive. Generally speaking, such water-soluble polymers will also be acceptable for use with food additives, cosmetic additives and agrochemicals (agricultural chemicals), since the most stringent requirements are usually placed on pharmaceuticals, particularly for parenteral use. Conversely, however, a polymer which is not pharmaceutically acceptable could, for example, nevertheless be agriculturally acceptable, particularly for non-crop applications; such a polymer is intended for use herein in compositions with those non-drug materials, e.g. agrochemicals, which do not require pharmaceutical acceptability. Similarly, the water-soluble polymers for use with food and cosmetic additives need only be acceptable for use in foods and cosmetics.

As lipophilic and/or water-labile food additives which are contemplated for use in the methods and com-

positions of the present invention, there can be mentioned, by way of example, flavoring agents, preservatives, antioxidants, sweetening agents, and coloring agents. Illustrative of such additives are flavors such as vanillin, aromatic flavoring oils such as lemon oil, cinnamon oil, oil of anise, oil of bitter almond or benzaldehyde, oil of clove, oil of orange, oil of peppermint, garlic oil, onion oil and menthol; sweeteners such as aspartame and saccharin; colors such as methyl yellow as well as natural colors; preservatives such as methylparaben, propylparaben, chlorbutol, benzoic acid and salicylic acid; and antioxidants such as butylated hydroxyanisol.

In the case of cosmetic additives contemplated for use in the methods and compositions of this invention, many of the same classes of ingredients (including some of the same specific ingredients) noted above as food additives are intended. Illustrative classes of cosmetic additives include preservatives, antioxidants, aromatic oils (fragrances), coloring agents and vitamins (also noted as drugs herein). Specific additives of interest for cosmetics include fragrant aromatic oils such as lavender oil, pine oil, oil of geranium, oil of rose, oil of sweet bay, oil of lemon, oil of lemon grass, preservatives such as camphor and vitamins such as vitamin D_2 (cholecalciferol), vitamin D_3, vitamin A and vitamin E.

With regard to agrochemicals, those contemplated for use in the methods and compositions of this invention include pesticides (including, for example, insecticides and nematocides), fungicides, herbicides and plant growth regulators. Illustrative of such agrochemicals are pesticides such as pentachlorophenol, mevinphos, piperonyl butoxide, hydroprene, methoprene and kinoprene; fungicides such as 4-chloro-3-methylbenzothiazolone and pyrrolnitrin; and herbicides such as pentachlorophenol and 2,6-dichlorobenzonitrile.

It is well-known that a number of food and cosmetic additives, particularly flavors, fragrances and colors, as well as agrochemicals (pesticides, herbicides, insecticides and fungicides) can be complexed with cyclodextrin. Such materials exhibit significantly increased complexation and water solubility, however, when used in the methods and compositions of the present invention.

Among the lipophilic and/or water-labile drugs which are contemplated for use in the methods and compositions of the present invention, there can be mentioned antineoplastics (anticancer/antitumor agents), sedatives, anti-inflammatory steroids (glucocorticoids), tranquilizers, anticonvulsants, antivirals, antihistaminics, vitamins/nutritional factors, emetics, anticoagulants, cardiotonics (including cardiac glycosides), diuretics, non-steroidal analgesic and/or anti-inflammatory agents (NSAID's), androgens, estrogens, anabolic agents, vasodilators, antidepressants, antipsychotics, hypnotics, antifungals, progestins, antiprotozoals, anthelmintics, anesthetics, vasoconstrictors, hypoglycemics, antibacterials/antibiotics, and anti-infectives, platelet inhibitors, muscle relaxants, antiemetics, radiodiagnostics, antispasmodics, antiarrythmics, carbonic anhydrase inhibitors, gastrointestinal agents (including H_2-antagonists and other anti-ulcer agents), antihypertensives, serotonin antagonists, narcotic antagonists, narcotic agonists, mixed narcotic agonists-antagonists, pharmacologically active proteins such as peptide hormones, enzymes, antibodies and other biologically produced substances, anti-Parkinsonism/dopamineric agents and drugs for treating Alzheimer's disease.

It is now well-known that lipophilic and/or water-labile drugs which complex with cyclodextrin have the required shape and size to fit at least partially into the cavity of the hydrated cyclodextrin molecule; see, for example, Brauns and Müller European Patent No. 0149197 B1. Drugs whose water solubility can be improved by complexation with cyclodextrins exhibit significantly increased complexation and water solubility when treated in accord with the present invention.

Specific drugs contemplated for use in the methods and compositions of the present invention include antineoplastics such as chlorambucil, lomustine, melphalan, methotrexate, hexamethylmelamine, teniposide, etoposide, semustine (methyl CCNU), fazarabine (Ara-AC), mercaptopurine, tubulazole, carmofur, carmustine, amsacrine, doxorubicin, bruceantin, diaziquone, dideminin B, echinomycin and PCNU; anti-inflammatory steroids such as betamethasone, fludrocortisone, dexamethasone, cortisone, hydrocortisone, triamcinolone, triamcinolone acetonide, prednisone and prednisolone; estrogens such as 17β-estradiol, 17α-ethynylestradiol (ethinylestradiol), ethynylestradiol 3-methyl ether, estrone, mestranol and estriol; progestins such as dimethisterone, norethindrone, norethindrone acetate, norgestrel, norethynodrel, ethisterone, medroxyprogesterone acetate and progesterone; anticonvulsants such as phenytoin (diphenylhydantoin) and carbamazepine; barbiturates such as pentobarbital, phenobarbital and secobarbital, variously useful as hypnotics, anticonvulsants and sedatives; antivirals such as vidarabine and virazole (also known as ribavirin); vitamins/nutritional factors such as retinol (vitamin A), vitamin A-acetate, cholecalciferol and retinal, as well as other fat-soluble vitamins such as the E, D and K vitamins; β-blockers such as timolol and atenolol, propranolol and nadolol; emetics such as apomorphine; diuretics such as chlorthalidone, furosemide and other sulfonamide-type diuretics and spironolactone, an aldosterone antagonist-type diuretic; anticoagulants such as dicumarol; cardiotonics such as digoxin and digitoxin; non-steroidal analgesics and/or anti-inflammatory agents such as aspirin, ibuprofen, indomethacin, piroxicam, sulindac and flurbiprofen; androgens such as 17-methyltestosterone and testosterone; mineral corticoids such as desoxycorticosterone; steroidal hypnotics/anesthetics such as alfaxalone; ana-

bolic agents such as fluoxymesterone and methanstenolone; antidepressants such as sulpiride; antibiotics such as ampicillin and penicillin G; anti-infectives, such as benzalkonium chloride, cetylpyridinium chloride and chlorhexidine; coronary vasodilators such as nitroglycerin, flunarizine, lidoflazine and mioflazine; hypnotics such as etomidate; carbonic anhydrase inhibitors such as acetazolamide, chlorzolamide, ethoxzolamine, methazolamide, L-671, 152 and MK-927; antifungals such as imidazole-type antifungals, e.g. econazole, clotrimazole, oxiconazole, bifonazole, metronidazole (metronidazole benzoate), fenticonazole, miconazole, sulconazole, tioconazole, isoconazole, butoconazole, ketoconazole, doconazole, parconazole, orconazole, valconazole and lombazole, and trizole-type antifungals, e.g. terconazole and itraconazole; antiprotozoals such as imidazole-type antiprotozoals, e.g. metronidazole, ornidazole, carnidazole, ipronidazole, tinidazole and nimorazole, and benzimidazole-type antifungals, e.g. flubendazole; H_2-antagonists, including those of the imidazole-type, e.g. burimamide, metiamide, cimetidine and oxmetidine; imidazole-type antineoplastics, such as tubulazole, a microtubule inhibitor; anthelmintic agents, including those of the benzimidazole-type, for example, thiabendazole, oxibendazole, cambendazole, fenbendazole, flubendazole, albendazole and oxfendazole; antihistaminics, including benzimidazoles such as astemizole, piperidines such as levocabastine and piperazines such as flunarizine, oxatomide and cinnarizine; antipsychotics, including those of the piperidine-type such as fluspirilene, pimozide and penfluridole; gastrointestinal agents, including piperidine derivatives such as loperamide and cisapride; serotonin antagonists, for example those of the piperidine-type such as ketanserin, ritanserin and altanserin, and those of the piperazine-type such as mianserin (also an antihistaminic); anesthetics such as lidocaine; hypoglycemics such as acetohexamide; anti-emetics such as dimenhydrinate; antibacterials such as co-trimoxazole; dopaminergic agents such as L-DOPA; anti-Alzheimer's agents such as THA; famotidine, an anti-ulcer agent/H_2-antagonist; benzodiazepines, for example chlordiazepoxide, diazepam, medazepam, oxazepam, lorazepam, flunitrazepam, estazolam, flurazepam, loprazolam, lormetazepam, nitrazepam, quazepam, temazepam and triazolam, variously useful as sedatives, hypnotics, anticonvulsants, tranquilizers and muscle relaxants; and prostaglandins, for example PGE's such as PGE_1 (alprostadil), a vasodilator, and PGI_2 (prostacyclin or epoprostenol), a platelet inhibitor.

In one particularly preferred aspect of the present invention, the drug contemplated for use herein is a carbonic anhydrase inhibitor, especially acetazolamide.

In another preferred aspect of the invention, the drug contemplated for use herein is a steroid, particularly an anti-inflammatory steroid (glucocorticoid), or a steroidal estrogen, progestin, anabolic agent, androgen, anesthetic/hypnotic or diuretic/aldosterone antagonist.

In another preferred aspect of the invention, the drug contemplated for use herein is a benzodiazepine sedative or an anti-infective agent.

In yet another preferred aspect of the invention, the drug contemplated for use herein is the reduced, dihydropyridine form of a dihydropyridine ⇄ pyridinium salt redox system for brain-targeted drug delivery.

With respect to the redox system for brain-targeted drug delivery, the following definitions are applicable:

The term "lipoidal" is intended to designate a redox moiety which is lipid-soluble or lipophilic.

The terms "redox carrier system" and "redox analog system" are intended to designate two different approaches to targeting drugs to the brain using a dihydropyridine ⇄ pyridinium salt system; compounds representing either of these approaches are contemplated for use in the present invention.

The redox carrier system provides for brain-targeted drug delivery by means of carrier-drugs, which in their reduced form, which is the form intended for administration, can be represented by the formula

[D-DHC]

wherein [D] is a centrally acting drug species and [DHC] is the reduced, biooxidizable, blood-brain barrier penetrating, lipoidal form of a dihydropyridine ⇄ pyridinium salt redox carrier. In their oxidized form, which is the form "locked" in the brain from which the active drug is ultimately released, the carrier-drugs can be represented by the formula

$$[D\text{-}QC]^+ X^-$$

wherein X^- is the anion of a non-toxic pharmaceutically acceptable acid, [D] is a centrally acting drug species and $[QC]^+$ is the hydrophilic, ionic pyridinium salt form of a dihydropyridine ⇄ pyridinium salt redox carrier. The various redox approaches are now well-known, having been described in many patents and literature articles; the originator of the redox technology, Nicholas S. Bodor, has also described the use of cyclodextrin derivatives in conjunction with the reduced, dihydropyridine forms of the redox systems, e.g. in Bodor United States Patents No. 4,983,586; 5,002,935; 5,017,566; and 5,024,998. While the redox systems for use herein can be any of those defined in the Bodor patents, those in which the centrally acting drug species and redox carriers are indicated in the Bodor patents as being preferred are likewise preferred for use herein. Thus, preferred redox carrier compounds of the formula [D-DHC] are those in which [D], the centrally acting drug species, is a dopaminergic agent, an androgenic agent, an anticonvulsant, an anxiolytic agent, a neurotransmitter, an antibiotic or antibacterial agent, an antidepressant, an antiviral agent, an anticancer or antitumor agent, an anti-

inflammatory agent, an estrogen or a progestin, particularly when the centrally acting drug species is dopamine, testosterone, phenytoin, GABA, valproic acid, tyrosine, methicillin, oxacillin, benzylpenicillin, cloxacillin, dicloxacillin, desipramine, acyclovir, trifluorothymidine, zidovudine, hydroxy-CCNU, chlorambucil, tryptamine, dexamethasone, hydrocortisone, ethinyl estradiol, norethindrone, estradiol, ethisterone, norgestrel, estrone, estradiol 3-methyl ether, estradiol benzoate, norethynodrel, mestranol, indomethacin, naproxen, FENU, HENU or 5-FU. Especially preferred redox carrier compounds of the formula [D-DHC] are:

1-methyl-3-{{N-{β-[3,4-bis(pivalyloxy)phenyl]ethyl}carbamoyl}}-1,4- dihydropyridine, 1-methyl-3-{N-[[β-[3,4-bis(isobutyryloxy)phenyl]-ethyl]]}carbamoyl-1,4-dihydropyridine and N-{β-[3,4-bis(pivalyloxy)-phenyl]ethyl}aminocarbonyloxymethyl 1,4-dihydro-1-methyl-3-pyridinecarboxylate, which are dopamine derivatives;

17β-[(1,4-dihydro-1-methyl-3-pyridinylcarbonyl)oxy]androst-4-en-3-one and 17β-{[(3"-carbamoyl-1',4'-dihydropyridinyl)acetyl]oxy}androst-4-en-3-one, which are testosterone derivatives;

5,5-diphenyl-3-[(1-methyl-1',4'-dihydropyridin-3'-yl)carbonyloxymethyl]-2,4-imidazolidinedione, 3-[(3'-carbamoyl-1',4'-dihydropyridin-1'-yl)acetyloxymethyl]-5,5-diphenyl-2,4-imidazolidinedione and 3-[3'-(3"-carbamoyl-1",4"-dihydropyridin-1"-yl)propionyloxymethyl]-5,5-diphenyl-2,4-imidazolidinedione, which are phenytoin derivatives;

1-methyl-3-N-[3-(benzyloxycarbonyl)propyl]carbamoyl-1,4-dihydropyridine and 1-methyl-3-{N-[(3'-cyclohexylcarbonyl)propyl]}-carbamoyl-1,4-dihydropyridine, which are GABA derivatives;

1-methyl-3-[2'-(2"-propyl)pentanoyloxy]ethylcarbamoyl-1,4-dihydropyridine, 1-methyl-3-[2'-(2"-propyl)pentanoyloxy]ethoxycarbonyl-1, 4-dihydropyridine and 1-[2'-(2"-propyl)pentanoyloxy]ethyl-3-carboxamide-1,4-dihydropyridine, which are valproic acid derivatives;

1-methyl-3-{N-[(1'-ethoxycarbonyl)-2'-(4"-pivaloyloxyphenyl)ethyl]}-carbamoyl-1,4-dihydropyridine and 1-methyl-3-{N-[(1'-ethoxycarbonyl)-2'-(4"-isobutyryloxyphenyl)ethyl]}carbamoyl-1,4-dihydropyridine, which are tyrosine derivatives;

[[(1,4-dihydro-1-methyl-3-pyridinyl)carbonyl]oxy]methyl [2S-(2α, 5α ,6β)]-3,3-dimethyl-7-oxo-6-[(2,6-dimethoxy)benzamido]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate, [[(1,4-dihydro-1-methyl-3 - pyridinyl)carbonyl]oxy]methyl [2S-(2α,5α,6β)]-3,3dimethyl-6-(5-methyl-3-phenyl-4-isoxazolecarboxamido-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate, [[(1,4-dihydro-1-methyl-3-pyridinyl)carbonyl]oxy]methyl [2S-(2α, 5α,6β)]-3,3dimethyl-7-oxo-6-[(phenylacetyl)amino]-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylate, [[(1,4-dihydro-1-methyl-3-pyridinyl)carbonyl]-oxy]methyl [2S-(2α,5α,6β)]-6-[3-(2-chlorophenyl)-5-methyl-4-isoxazolecarboxamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate and [[(1,4-dihydro-1-methyl-3-pyridinyl)carbonyl]oxy]methyl [2S-(2α,5α,6β)]-6-[3- (2,6-dichlorophenyl)-5-methyl-4-isoxazolecarboxamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2 carboxylate, which are derivatives of methicillin, oxacillin, benzylpenicillin, cloxacillin and dicloxacillin, respectively;

[{N-[3-(10,11-dihydro-5H-dibenz(b,f]azepin-5-yl)]propyl-N-methylamino}carbonyloxy]methyl 1,4-dihydro-1-methyl-3-pyridinecarboxylate and [1-{N-[3-(10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)]propyl-N-methylamino}carbonyloxy]ethyl 1,4-dihydro-1-methyl-3-pyridinecarboxylate, which are derivatives of desipramine;

1-methyl-3-{[2-(9-guanylmethoxy)ethoxy]carbonyl}-1,4-dihydropyridine, which is a derivative of acyclovir;

3'-(1,4-dihydro-1-methyl-3-pyridinylcarbonyl)-5'-pivaloyltrifluoro-thymidine, which is a derivative of trifluorothymidine;

3'-azido-3'-deoxy-5'-(1-methyl-1,4-dihydro-3-pyridinyl)-carbonyl]thymidine, which is a derivative of zidovudine (AZT);

N-(2-chloroethyl)-N'-[4-(1,4-dihydro-1-methyl-3-pyridinecarbonyloxy)-cyclohexyl]-N-nitrosourea, N-(2-fluoroethyl)-N'-[2-(1,4-dihydro-1-methyl-3-pyridinecarbonyloxy)ethyl]-N-nitrosourea and N-(2-chloroethyl)-N'-[2-(1,4-dihydro-1-methyl-3-pyridinecarbonyloxy)ethyl]-N-nitrosourea, which are derivatives of hydroxy-CCNU, FENU and HENU, respectively;

1-methyl-3-[(N-{2-[4-({4-[bis(2-chloroethyl)]amino}phenyl)-butanoyloxy]ethyl})carbamoyl]-1,4-dihydropyridine, 1-methyl-3-(N-{4-[4-(4-{[bis(2-chloroethyl)]amino}phenyl)butanoyloxy]cyclohexyl}carbamoyl)-1,4-dihydropyridine, 1-methyl-3-[(N-{2-[4-({4-bis(2-chloroethyl)]amino}- phenyl)butanoyloxy]propyl})carbamoyl]-1,4-dihydropyridine, 1-methyl-3-[(N-{2-phenyl-2-({4-[bis(2-chloroethyl)]amino}phenyl)butanoyloxy]}ethyl)-carbamoyl]-1,4-dihydropyridine and 1-methyl-3-[N-({1-[4(4-{[bis(2-chloroethyl)]amino}phenyl)butanoyloxy]cyclohexyl}methyl)carbamoyl]-1,4-dihydropyridine, which are derivatives of chlorambucil;

1-methyl-3-N-[2-(3-indolyl)ethyl]carbamoyl-1,4-dihydropyridine, which is a derivative of tryptamine;

9-fluoro-11β,17-dihydroxy-16α-methyl-21-{[(1-methyl-1,4-dihydropyridin-3-yl)carbonyl]oxy}pregna-1,4-diene-3,20-dione and 11β,17-dihydroxy-21-{[(1-methyl-1,4-dihydropyridin-3-yl)carbonyl]oxy}pregn-4-ene-3,20-dione, which are derivatives of dexamethasone and hydrocortisone, respectively;

3-hydroxy- 17,β-[(1-methyl-1,4dihydropyridin-3-yl)carbonyl]oxyestra-1,3,5(10)-triene, which is an estradiol derivative;

3-hydroxy-17β-{[1-methyl-1,4-dihydropyridin-3-yl)carbonyl]oxy}-19-nor-17α-pregna-1,3,5(10)-trien-20-yne, 3-[(1-methyl-1,4-dihydro-3-pyridinyl)carbonyloxy]estra-1,3,5(10)-trien-17-one, 17β-[(1-methyl-1,4-dihydro-3-pyridinyl)carbonyloxy]estra-1,3,5(10)-trien-3-ol 3-methyl ether, 3,17β-bis-{[(1-methyl-1,4-dihydropyridin-3-yl)carbonyl]oxy}estra-1,3,5(10)-triene, 3-(phenylcarbonyloxy)-17β-{[(1-methyl-1,4-dihydropyridin-3-yl)carbonyl]oxy}estra-1,3,5(10)-triene and 3-methoxy-17β-{[1-methyl-1,4- dihydropyridin-3-yl)carbonyl]oxy}-19-nor-17α-pregna-1,3,5(10)-trien-20-yne, which are derivatives of ethinyl estradiol, estrone, estradiol 3-methyl ether, estradiol, estradiol benzoate and mestranol, respectively;

17β-{[(1-methyl-1,4-dihydropyridin-3-yl)carbonyl]oxy}-19-norpregn-4-en-20-yn-3-one, 17β-{[(1-methyl-1,4-dihydropyridin-3-yl)carbonyl]oxy}pregn-4-en-20-yn-3-one, 13-ethyl-17β-{[(1-methyl-1,4-dihydropyridin-3-yl)carbonyl]oxy}-18,19-dinorpregn-4-en-20-yn-3-one and 17β-{[(1-methyl-1,4-dihydropyridin-3-yl)carbonyl]oxy}-19-norpregn-5(10)-en-20-yn-3-one, which are derivatives of norethindrone, ethisterone, norgestrel and norethynodrel, respectively;

1-methyl-3-[N-(2-{1-(p-chlorobenzoyl)-5-methoxy-2-methyl-3-indolyl]acetoxy}ethyl)carbamoyl]-1,4-dihydropyridine and 1-methyl-3-{N-[2-(6-methoxy-α-methyl-2-naphthalenylacetoxy)ethyl]carbamoyl-1,4-dihydropyridine, which are derivatives of indomethacin and naproxen, respectively; and

3-(1,4-dihydro--1-methyl-3-pyridinylcarbonyloxymethyl)-5-fluorouracil and 1-(1,4-dihydro-1-methyl-3-pyridinecarbonyloxymethyl)-5-fluorouracil, which are derivatives of 5-FU (5-fluorouracil).

In the discussion that follows, the particulars of the present invention are discussed with respect to drugs. It is to be understood, however, that except where the discussion focuses on matters which are obviously unique to drugs (such as bioavailability), the particulars are the same when a food additive, cosmetic additive or agrochemical is used instead of a drug herein.

Quite surprisingly, it has now been found that is possible to increase the effects of cyclodextrin complexation by adding small amounts of water-soluble, pharmaceutically acceptable, pharmacologically inactive polymers to aqueous cyclodextrin/drug solutions and then heating the solutions for some time. Typically, the polymer is dissolved in an aqueous solution of the cyclodextrin, or both polymer and cyclodextrin are dissolved in water, and then the drug is added. The cyclodextrin concentration can range from about 0.1 to 70% w/v and the polymer concentration from about 0.001 to about 5% w/v, preferably from about 0.01 to about 0.5% w/v, in the original solution. The polymer: cyclodextrin weight ratio can range from about 1:4 to about 1:50,000, but is usually from about 1:100 to about 1:10,000, that is, 1 part of polymer to 100 to 10,000 parts of cyclodextrin, and is even more preferably from about 1:500-5,000, i.e. 1 part of polymer to from 500 to 5,000 parts of cyclodextrin. Since maximum complexation is ordinarily desired, the drug is usually added in excess. The drug may be dissolved in the cyclodextrin/polymer solution before, during and/or after the cyclodextrin solution has been kept at from about 30 to about 150°C for a period of from about 0.1 to about 100 hours. Optionally, the polymer and cyclodextrin can be combined in aqueous solution, with heating at the temperature and for the time indicated in the preceding sentence and dried (preferably lyophilized) to give a cyclodextrin/polymer combination complexing agent. That complexing agent can subsequently be combined in aqueous solution with the drug, with or without heating for the time and at the temperature indicated above. Whatever the manner of preparing the drug/cyclodextrin/polymer aqueous solution, said solution can optionally be dried in accord with methods which are known per se. Depending on the drug employed, acid or base may be added to the cyclodextrin/polymer/drug solution during preparation.

As will be apparent from the Examples hereinafter, one can readily determine the concentration at which a given water-soluble polymer exerts a maximum solubilizing/stabilizing/complexing effect on a given drug and a given cyclodextrin in aqueous medium. It is generally disadvantageous to use a significant amount of polymer in excess of that needed to achieve the maximum effect. Excess polymer can actually decrease the desired solubilizing/stabilizing/complexing effect, and can tend to increase the viscosity of the aqueous medium in which complexation occurs. The amount of polymer used should be sufficient to enhance stabilization/solubilization/complexation, but insufficient to cause a significant increase in viscosity upon heating. Increase in viscosity to a gel-like or near gel-like stage should be avoided when carrying out the stabilization/solubilization/complexation processes of the invention. Obviously, once the process has been completed, the resultant mixture can be made more viscous if desired in the pharmaceutical or other compositions provided by the present invention.

Aqueous solutions of cyclodextrins and polymers prepared in accord with the present invention have a greater solubilizing and stabilizing effect on lipophilic and/or water-labile drugs than cyclodextrin solutions made by simply dissolving cyclodextrins in water or aqueous buffer solutions. The water-soluble pharmaceutical polymers increase the solubilizing effect of the cyclodextrins and, thus, make it possible to reduce the amount of cyclodextrin which will be present in the pharmaceutical composition ultimately administered. Aqueous cyclodextrin drug formulations containing water-soluble pharmaceutical polymers are characterized by fast and efficient drug release, which can result in a more rapid onset of the desired therapeutic response and

better total bioavailability of the drugs. Solid pharmaceutical preparations, made, for example, by removal of water from the above-mentioned aqueous cyclodextrin-polymer-drug solutions, for example by lyophilization, are characterized by faster and more efficient dissolution of drugs compared to the dissolution of drugs from solid cyclodextrin preparations without polymers. This can lead to hastening the onset of the therapeutic response and can also increase the total bioavailability of drugs from solid pharmaceutical preparations.

It appears that the water-soluble polymers used in accord with the present invention alter the hydration of the cyclodextrin molecules and thus their three-dimensional structure in aqueous solutions. Heating accelerates this process. It also appears that the polymer participates directly in the drug complex formation, acting as a co-complexing agent with the cyclodextrin. S.H.S. Leung, J.R. Robinson and V.H.L. Lee ["Parenteral Products", Chapter 10 in *Controlled Drug Delivery. Fundamentals* and *Applications,* second edition, J.R. Robinson and V.H.L. Lee, editors, Marcel Dekker, Inc., New York, 1987, pp.433-480], in a review of studies from the 1950's and early 1960's, point out that the role of plasma protein and tissue binding in prolonging drug action is well-known, and that the same result can be achieved by forming a dissociable complex of a drug with macromolecules such as methylcellulose, carboxymethylcellulose and polyvinylpyrrolidone. **Table 1** and **Table 6** hereinbelow show that aqueous polymer solutions (S_2) solubilize drugs to a greater extent than pure water (S_1). This can be attributed to complexation of the drug with the polymer. Thus, the polymers and the cyclodextrins both form soluble complexes with various drug molecules and can be used to increase the aqueous solubility of the drugs. However, when polymer and cyclodextrin are mixed together in accord with the present invention, one obtains greater drug solubility enhancement than when the polymer and cyclodextrin are used separately; indeed, the combination effect is more than simply additive, it is synergistic. This is indicative of the formation of a new type of complex between the drug and the polymer-cyclodextrin. The cyclodextrin can thus be considered to be the complexing agent, the polymer a co-complexing agent, and the drug complex not simply a drug/cyclodextrin complex, but a drug/cyclodextrin/ polymer co-complex.

Pharmaceutical compositions utilizing the drug/cyclodextrin/polymer products prepared in accord with the present invention can be used to treat a variety of conditions, depending upon the pharmacological nature of the drug selected for administration. The compositions contain a pharmacologically/ therapeutically effective amount of the selected drug and the amounts/ratios of selected cyclodextrin and selected polymer noted hereinabove, together with a non-toxic, pharmaceutically-acceptable carrier. For example, if the selected drug is an anti-inflammatory agent, a pharmacologically effective amount thereof will be an amount sufficient to elicit an anti-inflammatory response. Selection of the cyclodextrin and the polymer in the compositions will depend upon the nature of the drug and the contemplated route of administration. Virtually any route of administration by which a selected drug can be used can be employed for the instant compositions, including but not limited to parenteral, oral and topical (including ophthalmic) routes. Polymers and cyclodextrins as defined herein will be selected according to the contemplated route of administration, since some may be acceptable for certain routes of administration and not for others. For example, a hydroxyalkylated cyclodextrin such as hydroxypropyl-β-cyclodextrin rather than an alkylated cyclodextrin would be selected for intravenous use because of toxicity considerations. Similarly, only some of the polymers disclosed herein may be suitable for intravenous use, as is indeed well-known in the art.

In the case of parenteral formulations, intended, for example, for intramuscular, subcutaneous, intra-articular or intravenous administration, the pharmaceutical composition of drug/cyclodextrin/polymer will be in the form of an aqueous solution which is acceptable for parenteral administration, i.e. which is sterile and pyrogen-free and has been prepared in accord with accepted pharmaceutical procedures, for example as described in *Remington's Pharmaceutical Sciences,* seventeenth edition, ed. Alfonso R. Gennaro, Mack Publishing Company, Easton, PA (1985), pp. 1518-1552. The aqueous sterile injection solutions may further contain antioxidants, buffers, bacteriostats, isotonicity adjusters and like additions acceptable for parenteral formulations. Various unit dose and multidose containers, e.g. sealed ampules and vials, may be used, as is well-known in the art. The essential ingredients of the sterile parenteral formulation, i.e. the drug(s), water and selected cyclodextrin(s) and polymer(s) may be presented in a variety of ways, just so long as the solution ultimately administered to the patient contains the appropriate amounts of the essential ingredients. Thus, for example, the drug/cyclodextrin/polymer/ water formulation may be presented in a unit dose or multidose container, ready for injection. As another example, a concentrated solution of drug/cyclodextrin/polymer/water may be presented in a separate container from a diluting liquid (water or cyclodextrin/water) designed so that the contents can be combined to give a formulation containing appropriate amounts for injection. As another alternative, the drug or a drug/cyclodextrin/polymer combination may be provided in a freeze-dried condition in one container, while a separate container contains diluting liquid (water or cyclodextrin/water, depending on the amount of cyclodextrin in the other container), again designed so that the contents can be combined to give a formulation containing the appropriate amounts of the essential ingredients. As yet another alternative, the cyclodextrin/polymer may be provided in a freeze-dried condition in one container, the drug in another and the di-

luting liquid in yet another container. In any event, the contents of each container will be sterile.

For oral administration, the pharmaceutical compositions may be in the form of any well-known oral dosage form, e.g. tablets, caplets, capsules, pills, powders, solutions, gels and the like. Orally acceptable carrier materials, including excipients, binders and disintegrators, are well-known in the art. Moreover, the usual buffers, coloring agents, flavoring agents and sweetening agents can be added, if necessary or if desired. Tablets and caplets may also be coated with the usual coating materials.

In addition to oral dosage forms which are intended to be swallowed, the present invention contemplates oral dosage forms which are intended for usage only in the oral cavity, typically mouthwashes, and those which are intended for buccal and/or sublingual administration (such as lozenges).

For rectal or vaginal administration, suppositories may be suitable, appropriate carriers for which are well-known. Similarly, for topical use, well-known topically acceptable carriers/vehicles can be employed to form creams, gels, ointments and the like. Appropriate carriers for use in nasal dosage forms (solutions, gels, ointments and the like) are similarly well-known.

In the case of ophthalmic compositions, the carrier must be a non-toxic, ophthalmically acceptable carrier. Suitable ophthalmic carriers will be apparent to those skilled in the art of ophthalmic formulations. Obviously, the choice of suitable carriers will depend on the exact nature of the particular dosage form desired, e.g. whether the drug/cyclodextrin/polymer complex is to be formulated into an ophthalmic solution or suspension (typically for use as eye drops), an ophthalmic ointment or cream or an ophthalmic gel. Preferred dosage forms are solutions, which contain a major amount of water in addition to the active ingredient. Minor amounts of other ingredients such as pH adjusters (e.g. a base such as NaOH), emulsifiers or dispersing agents, buffering agents, preservatives, wetting agents and jelling agents may also be present. Most preferably, the ophthalmic composition is a sterile, isotonic, buffered aqueous solution.

Especially preferred pharmaceutical compositions provided by the present invention include ophthalmic formulations (e.g. eyedrops) containing a carbonic anhydrase inhibitor, such as acetazolamide; oral formulations such as mouthwashes or buccal tablets containing an anti-inflammatory steroid, e.g. hydrocortisone, dexamethasone or triamcinolone acetonide; oral formulations such as sublingual tablets containing a benzodiazepam such as flunitrazepam, for treatment of insomnia; and sublingual tablets comprising an estrogen, progestin or androgen (such as 17β-estradiol for treatment of post-menopausal symptoms in women) or an anti-infective agent (e.g. benzalkonium chloride).

Generally speaking, the therapeutic dosage ranges for administration of drugs in the pharmaceutical formulations described herein will be the same as or less than (in some instances, substantially less than) those characteristically used for administration of the drug *per se* (or, in the case of the carrier-drugs, of the parent drug species *per se*). Naturally, such therapeutic dosage ranges will vary with the size and species of the patient, the condition for which the formulation is administered, the route of administration employed and the like. The quantity of given dosage form needed to deliver the desired dose of active ingredients will of course depend upon the concentration of the drug in the pharmaceutical formulation.

In a similar manner to the pharmaceutical compositions described above, compositions comprising the non-drug/cyclodextrin/polymer products prepared according to the present invention will be formulated in accord with their intended use. A non-toxic, pharmaceutically acceptable carrier as used in the instant pharmaceutical compositions will normally meet or exceed the requirements for use in cosmetics, agrochemicals and even in foods. Such a carrier is therefore eminently well-suited for cosmetic, food and agricultural applications as well. Yet other carriers can be used for these other applications, however, just so long as they are acceptable for use in foods or cosmetics or agrochemicals, as the case may be. Thus, for example, an agriculturally acceptable carrier will be used with an agrochemical/cyclodextrin/polymer product, which will itself be present in an effective amount, i.e. a herbicidally effective amount when the agrochemical is a herbicide, a pesticidally effective amount when the agrochemical is a pesticide, a fungicidally effective amount when the agrochemical is a fungicide, and so forth. Appropriate carrier materials for use with food additives or cosmetic additives or agrochemicals, in addition to non-toxic, pharmaceutically acceptable carriers, will be apparent to those skilled in the food, cosmetic and agrochemical arts.

In order to further illustrate the present invention and the advantages thereof, the following specific examples are given, it being understood that same are intended only as illustrative and in no way limitative of the invention.

Example 1

Solubilities (S) of various drugs in four different solvents, i.e. (a) water (S_1), (b) aqueous 0.25% (w/v) sodium carboxymethylcellulose solution (CMC) (S_2), (c) aqueous solution of 10% (w/v) 2-hydroxypropyl-β-cyclodextrin (HPβCD) of molar substitution (MS) = 0.6 (S_3) and (d) aqueous solution containing both 0.25% (w/v) CMC and

10% (w/v) HPβCD MS = 0.6 (S_4) were determined by adding an excess amount of the drug to be tested to the solvents and heating the suspensions formed in sealed containers to 120°C. The suspensions were kept at this temperature for 20 minutes and then allowed to equilibrate for 3 days at room temperature (approximately 23°C). After equilibration, aliquots were filtered through 0.45 µm membrane filters, diluted with a mixture of methanol and water (7:3 v/v) and analyzed by an high pressure liquid chromatographic (HPLC) method. The results set forth in **Table 1** show that the solubilizing effect of HPβCD was increased by 4 to 57% (S_4/S_3 = 1.04 to 1.57) when 0.25% CMC was present in the solution.

Table 1

The effect of CMC on the solubilization of various drugs in aqueous HPβCD solutions.

Drug	S_1 (mg/ml)	S_2 (mg/ml)	S_3 (mg/ml)	S_4 (mg/ml)	S_4/S_3
Acetazolamide	0.70	0.84	2.52	3.11	1.23
Alprazolam	0.07	0.18	1.28	1.55	1.21
Carbamazepine	0.11	0.20	7.00	9.20	1.31
Clotrimazole	0.00	0.00	1.20	1.40	1.17
Dexamethasone	0.26	0.33	8.43	8.75	1.04
Diazepam	0.69	0.81	9.14	9.70	1.06
Econazole	0.57	0.60	4.86	7.41	1.52
17β-Estradiol	0.01	0.17	5.10	5.35	1.05
Ethoxyzolamide	0.04	0.07	1.19	1.66	1.39
Hydrocortisone	0.36	1.10	12.88	17.02	1.32
Miconazole	0.04	0.06	1.98	2.50	1.26
Oxazepam	0.03	0.04	0.90	1.42	1.57

Table 1 -- continued

Drug	S_1 (mg/ml)	S_2 (mg/ml)	S_3 (mg/ml)	S_4 (mg/ml)	S_4/S_3
Prednisolone	0.38	0.53	13.60	15.30	1.13
Progesterone	0.00	0.00	4.03	6.11	1.52
Sulfamethoxazole	0.36	0.69	10.01	12.60	1.26
Termazepam	0.60	0.65	3.01	3.48	1.16
Triamcinolone acetonide	0.03	0.07	2.09	2.58	1.23

Example 2

The effect of increasing CMC concentration on the solubility of three drugs in aqueous 10% (w/v) HPβCD MS = 0.9 solution was also determined under the same condition as in **Example 1**. The results are shown in **Table 2.**

Table 2

The effect of increasing CMC concentration on solubilization.

Drug	0.00% CMC (w/v)	0.10% CMC (w/v)	0.25% CMC (w/v)	0.50% CMC (w/v)
Acetazolamide	2.52	3.60	3.21	3.75
Hydrocortisone	12.88	15.97	15.78	18.70
Oxazepam	0.90	1.49	1.31	1.88

Example 3

The effect of heating on the solubilization of hydrocortisone in aqueous solution containing 10% (w/v)

HPβCD MS = 0.6 and 0.25% (w/v) CMC was investigated as follows: An excess amount of hydrocortisone was added to the solution and the suspension which was formed was heated to 120°C in a sealed container. The suspension was kept at this temperature for (a) 20, (b) 40, (c) 60 and (d) 80 minutes. At each time point, an aliquot of the suspension was removed and allowed to equilibrate for 3 days at room temperature (approximately 23°C). After equilibration, each aliquot was filtered through a 0.45 μm membrane filter, diluted with a mixture of methanol and water (7:3 v/v) and analyzed by HPLC. The results in **Table 3** show that the solubilizing effect of the HPβCD-CMC mixture increases with increasing duration of heating.

Table 3

The effect of heating on the solubilization of hydrocortisone. The solubility of hydrocortisone in aqueous 10% (w/v) HPβCD - 0.25% (w/v) CMC solution at room temperature.

	Duration of Heating (Minutes)			
	20	40	60	80
Solubility (mg/ml)	17.02	17.02	19.86	25.92

Example 4

Part A

The effect of polyvinylpyrrolidone (PVP) of molecular weight 360,000 on drug-cyclodextrin complexation

was investigated by determining the phase-solubility diagrams of hydrocortisone in aqueous 2-hydroxypropyl-β-cyclodextrin (HPβCD) of molar substitution (MS) 0.6 solutions and calculating the stability constant (K_c) for the complex from the slope and the solubility (S_o) of hydrocortisone in water ($1x10^{-3}$ mol/liter).

$$K_c = \text{slope} \times (S_o x(1\text{-slope}))^{-1}$$

An excess amount of the drug was added to water containing from 0 to 0.7% (w/v) PVP and varying amounts of HPβCD. The suspensions which formed were heated in sealed containers to 120°C and kept at that temperature for 22 minutes. After equilibration for at least three days at room temperature (approximately 22°C), aliquots of the suspensions were removed from the containers and each aliquot was filtered through a 0.45 μm membrane filter and analyzed by HPLC. The solubility of the drug was determined at least three times at each HPβCD and PVP concentration, and the slope of the phase-solubility diagram was determined by linear regression of the mean solubility versus HPβCD concentration values in mole per liter. The correlation coefficient (corr.) was calculated for each linear regression. The results are shown in **Table A** below.

Table A

The effect of PVP on the stability constant of the hydrocortisone-HPβCD MS 0.6 complex at room temperature (approx. 22°C).

PVP Concentration (% w/v)	Slope	Corr.	Kc (liter/mol)
0	0.502	0.988	1010
0.01	0.528	0.972	1120
0.025	0.532	0.994	1140
0.05	0.544	0.977	1190
0.1	0.591	0.999	1450
0.15	0.577	0.999	1360
0.2	0.548	0.999	1210
0.3	0.535	0.995	1150
0.4	0.537	0.996	1160
0.5	0.544	0.998	1190
0.6	0.561	1.000	1280
0.7	0.543	0.999	1190

The results in **Table A** show that it was possible to obtain over 40% increase (at 0.1% PVP concentration) in K_c by addition of PVP. The increase was concentration dependent and decreased somewhat upon further addition of PVP.

Part B

Comparable results were obtained when the effect of PVP on the solubilization of hydrocortisone by HPβCD MS 0.6 was investigated. The solubility of hydrocortisone was determined in aqueous 10% (w/v)

HPβCD MS 0.6 solutions containing from 0 to 0.4% (w/v) PVP (molecular weight 360,000). An excess amount of hydrocortisone was added to the aqueous 10% HPβCD solutions and the suspensions which formed were heated in sealed containers to 120°C and kept at that temperature for 22 minutes. After equilibration for at least three days at room temperature (approximately 22°C), aliquots of the suspensions were removed from the containers and each aliquot was filtered through a 0.45 μm membrane filter and analyzed by HPLC. The solubility of the drug was determined at least three times at each PVP concentration and the results are shown in **Fig. 1** (the mean values of three experiments ± the standard error of the mean).

Fig. 1 shows that a maximum solubilization of hydrocortisone in aqueous 10% (w/v) HPβCD MS 0.6 solution was obtained when 0.1 to 0.15% (w/v) PVP was present in the solution, and that the solubilization at the maximum was about 32% compared to aqueous 10% (w/v) HPβCD MS 0.6 solution containing no PVP. Similar results were obtained when other water-soluble polymers, e.g. carboxymethylcellulose and hydroxypropyl methylcellulose, were added to aqueous cyclodextrin solutions. Generally, a maximum solubilization was obtained when the polymer concentration was above 0.003% (w/v) but below 0.1 %, but this was dependent on the type of polymer added to the aqueous cyclodextrin solution, the chain length (or the molecular weight) of the polymer and the cyclodextrin concentration in the aqueous solution.

The maximum effect is obtained at a very low polymer concentration before the polymer has any real effect on the viscosity of the solution. For example, the viscosity of a solution containing 10% or less PVP is essentially the same as that of water *(Handbook of Pharmaceutical Excipients*, American Pharmaceutical Association and the Pharmaceutical Society of Great Britain, Washington, 1986, pp. 234-239). Also, this increased solubilization (i.e. complexation) is a stable condition. The increased drug solubility frequently observed in viscous aqueous solutions, that is, formation of supersaturated drug solution, is an unstable condition which usually returns to a stable condition (under precipitation of the drug) within a few hours from its formation (Uekama et al., *J. Incl Phenomena*, **1**, 309-312, 1984). Thus, this increased complexation in the presence of a very small amount of a water-soluble polymer is not directly related to increased viscosity of the aqueous solution.

Example 5

Solubilities (S) of three drugs in four different solvents, i.e. (a) water (S_1), (b) aqueous 0.25 % (w/v) sodium carboxymethylcellulose solution (CMC) (S_2), (c) aqueous solution of 10% (w/v) hydroxyethyl-β-cyclodextrin (HEβCD) of molar substitution (MS) = 0.6 (S_3), and (d) aqueous solution containing both 0.25% (w/v) CMC and 10% (w/v) HEβCD MS = 0.6 (S_4), were determined as in **Example 1**. The results in **Table 4** show that the solubilizing effect of HEβCD was increased by 32 to 53% (S_4/S_3 = 1.32 to 1.53) when 0.25% (w/v) CMC was present in the solution.

Table 4

The effect of CMC on the solubilization of drugs in aqueous HEβCD solutions.

Drug	S_1 (mg/ml)	S_2 (mg/ml)	S_3 (mg/ml)	S_4 (mg/ml)	S_4/S_3
Hydrocortisone	0.36	1.10	17.51	26.81	1.53
Miconazole	0.04	0.06	2.51	3.31	1.32
Sulfamethoxazole	0.36	0.69	7.07	9.81	1.39

Example 6

Solubilities (S) of hydrocortisone in four different solvents, i.e. (a) water (S_1), (b) aqueous 0.25% (w/v) hydroxypropyl methylcellulose solution (HPMC) (S2), (c) aqueous solution of 5% (w/v) 2-hydroxypropyl- α-, β-, or γ-cyclodextrin (HPαCD, HPβCD, or HPγCD) of molar substitution (MS) = 0.6, 0.9 and 0.6, respectively, (S3), and (d) aqueous solution containing both 0.25% (w/v) HPMC and 5% (w/v) HPαCD, HPβCD, or HPγCD (S_4), were determined as in **Example 1**. The results in **Table 5** show that the solubilizing effect of the cyclodextrin derivative was increased by 10 to 50% (S_4 /S_3 = 1.1 to 1.5) when 0.25% HPMC was present in the solution.

Table 5

The effect of HPMC on the solubilization of hydrocortisone in aqueous cyclodextrin solutions.

Cyclodextrin	S_1 (mg/ml)	S_2 (mg/ml)	S_3 (mg/ml)	S_4 (mg/ml)	S_4/S_3
HPαCD MS = 0.6	0.4	1.4	2.4	3.6	1.5
HPβCD MS = 0.9	0.4	1.4	6.7	7.7	1.2
HPγCD MS = 0.6	0.4	1.4	7.7	8.7	1.1

Example 7

Solubilities (S) of three drugs in four different solvents, i.e. (a) water (S_1), (b) aqueous 0.25% (w/v) polyvinylpyrrolidone solution (PVP) (S_2), (c) aqueous solution of 10% (w/v) hydroxypropyl-β-cyclodextrin (HPβCD) of molar substitution (MS) = 0.7 (S_3), and (d) aqueous solution containing both 0.25% (w/v) PVP and 10% (w/v) HPβCD MS = 0.7 (S_4), was determined as in **Example 1**. The results in **Table 6** show that the solubilizing effect of HPβCD was increased by 27 to 129% (S_4/S_3 = 1.27 to 2.29) when 0.25% (w/v) PVP was present in the solution.

Table 6

The effect of PVP on the solubilization of drugs in aqueous HPβCD solutions.

Drug	S_1 (mg/ml)	S_2 (mg/ml)	S_3 (mg/ml)	S_4 (mg/ml)	S_4/S_3
Acetazolamide	0.70	1.05	2.80	3.66	1.31
Carbamazepine	0.11	0.31	6.43	7.50	1.17
Clotrimazole	0.00	0.00	1.20	1.80	1.50
Dexamethasone	0.26	0.33	7.53	8.00	1.06
Econazole	0.57	0.64	5.22	5.65	1.08
17β-Estradiol	0.01	-	5.10	9.50	1.86
Ethoxyzolamide	0.04	0.06	1.36	2.72	2.00
Miconazole	0.04	0.20	2.36	3.40	1.44
Progesterone	0.00	0.00	4.76	5.71	1.20
Oxazepam	0.03	0.04	0.90	1.14	1.27
Trimethoprim	0.82	1.35	2.83	6.47	2.29
Sulfamethoxazole	0.36	0.86	5.71	8.92	1.56

Example 8

Solubilities (S) of various drugs in eight different solvents, i.e. (a) water (S_1), (b) aqueous 10% (v/v) ethanol solution (S_2), (c) aqueous 0.25% (w/v) sodium carboxymethyl-cellulose solution (CMC) (S_3), (d) aqueous solution containing both 10% (v/v) ethanol and 0.25% (w/v) CMC (S_4), (e) aqueous solution of 10% (w/v) 2-hydroxypropyl-β-cyclodextrin (HPβCD) of molar substitution (MS) = 0.6 (S_5), (f) aqueous solution containing both 10% (v/v) ethanol and 10% (w/v) HPβCD MS = 0.6 (S_6), (g) aqueous solution containing both 0.25% (w/v) CMC and 10% (w/v) HPβCD MS = 0.6 (S_7), and (h) aqueous solution containing 10% (v/v) ethanol, 0.25% (w/v) CMC and 10% (w/v) HPβCD MS = 0.6 (S_8) were determined as in **Example 1.** The results in **Table 7** show that CMC

is also able to increase the solubilizing effect of HPβCD in aqueous ethanolic solutions.

Table 7

The effect of ethanol and CMC on the solubilizing effect of HPβCD in aqueous solutions.

Drug	Solubility (mg/ml)							
	S_1	S_2	S_3	S_4	S_5	S_6	S_7	S_8
Acetazolamide	0.70	1.11	0.84	0.75	2.52	2.19	3.11	2.50
Hydrocortisone	0.36	0.83	1.10	1.53	12.88	10.91	20.64	13.27
Miconazole	0.04	0.31	0.06	-	1.98	2.22	2.50	12.55

Example 9

The permeability through a semi-permeable membrane was investigated. Semipermeable cellophane membrane was placed in a Franz diffusion cell containing 10 ml aqueous 5% (w/v) HPβCD solution as the receptor phase. The donor phase consisted of a suspension of approximately 3% (w/v) hydrocortisone in (a) aqueous 10% (w/v) hydroxypropyl-β-cyclodextrin (HPβCD) solution and (b) aqueous solution containing both 10%

(w/v) HPβCD and 0.25% (w/v) carboxymethyl-cellulose (CMC), prepared as described in Example 1, and 2 ml of the donor phase applied to the membrane surface (area 3.1 cm^2). The assembled diffusion cells were kept at room temperature (22±1°C) and samples (30 µl) were removed from the donor phase every 10 minutes, up to 2 hours, and analyzed immediately by HPLC. The results shown in **Table 8** clearly indicate that hydrocortisone is released faster from a suspension containing CMC than from suspension containing no CMC.

Table 8

The solubility (S) and the flux (F) of hydrocortisone through a semi-permeable cellophane membrane from hydrocortisone suspensions in HPβCD vehicles.

Vehicle composition	S (mg/ml)	F (µg/cm^2/minute)
Aqueous (10%) (w/v) HPβCD solution	14.96	3.02
Aqueous solution containing 10% (w/v) HPβCD and 0.25% (w/v) CMC	19.23	5.36

Example 10

The effect of carboxymethylcellulose (CMC) on the release of hydrocortisone from tablets containing hydrocortisone-HPβCD complex was investigated.

The freeze-dried hydrocortisone-HPβCD complex was prepared by adding an excess of hydrocortisone to aqueous solution containing 50% (w/w) (about 58 % w/v) HPβCD and 0, 0.1 or 0.25% (w/v) CMC and heating the hydrocortisone suspensions formed for 20 minutes at 120°C. After equilibration for 3 days at room temperature, the suspensions were filtered through 0.45 μm membrane filters, the filtrates were lyophilized and the solid which formed was ground with a mortar and pestle. The amount of hydrocortisone incorporated into the HPβCD complex was determined by HPLC.

Individual disks of 200 mg hydrocortisone-HPβCD complex were compressed in a hydraulic press under vacuum and a force of $1x10^4$ kg for 1.5 minutes using a 13 mm (diameter) IR potassium bromide pellet punch. The disks had a cross-sectional area of 1.33 cm^2. Each disk contained approximately 27 mg of hydrocortisone.

The dissolution studies were carried out using a USP XXII described paddle apparatus for dissolution rate determination. The release rate was determined at 37±1°C and 100 rpm by adding one tablet to 900 ml of water. Samples were withdrawn at various time intervals, filtered through 0.45 membrane filters and analyzed by HPLC.

The results in **Fig. 2** show that hydrocortisone dissolves significantly faster from tablets containing hydrocortisone-HPβCD complex prepared in the presence of CMC than from tablets prepared in the absence of CMC. The results shown in **Fig. 2** are the average of four experiments. The dissolution tests were started at time zero. Three minutes later, 68.3% of the hydrocortisone had dissolved from tablets containing hydrocortisone-HPβCD complex formed without the addition of CMC, 74.2% of the hydrocortisone had dissolved from tablets containing hydrocortisone-HPβCD complex formed with the addition of 0.1% (w/v) CMC, and 81.0% of the hydrocortisone had dissolved from tablets containing hydrocortisone-HPβCD complex formed with the addition of 0.25% (w/v) CMC.

Example 11

Eye drops containing a carbonic anhydrase inhibitor, acetazolamide, were prepared the following way: Hydroxypropyl methylcellulose (HPMC), 0.25% (w/v), was dissolved in distilled water and hydroxypropyl-β-cyclodextrin MS = 0.6, 20% (w/v), benzalkonium chloride [0.02% (w/v)] and the sodium salt of ethylenediaminetetraacetic acid [EDTA, 0.1% (w/v)] were then dissolved in the aqueous HPMC solution. Finally, acetazolamide, 1% (w/v), was added to this solution and dissolved by heating in an autoclave (120°C for 20 min). The eye drop solution which formed was allowed to equilibrate at room temperature for one week.

The topical activity of the carbonic anhydrase inhibitor eye drop solution was evaluated in conscious white New Zealand rabbits of either sex (2.5 to 3.5 kg). The intraocular pressure was recorded by a pneumatic tonometer without local anaesthesia. The eye drop solution (0.1 ml) was placed on the cornea of the right eye (the left eye was used as control) and the intraocular pressure was recorded at various time intervals (**Fig. 3**).

Example 12

Hydrocortisone mouthwash was prepared in the following way: HPβCD MS = 0.6 (3.5% (w/v)), peppermint oil (0.05% (w/v)), ethanol (12% (v/v)), CMC (0.5% (w/v)), benzalkonium chloride (0.02% (w/v)) and the sodium salt of ethylenediaminetetraacetic acid (0.1% (w/v)) were dissolved in water and the solution was heated in a sealed container in an autoclave (120°C for 20 minutes). After equilibration to room temperature, hydrocortisone (0.3% (w/v)) was dissolved in the cyclodextrin solution.

The topical activity of the hydrocortisone mouthwash solution was evaluated as follows: Patients were selected on the basis of severe ulceration, causing considerable pain, discomfort, inconvenience with work and the like. Normally the patients had unsuccessfully tried numerous other remedies such as gentian violet, chlorhexidine, silver nitrate, hydrocortisone, and triamcinolone, from a variety of sources. Each patient washed his/her mouth with 5-10 ml of the hydrocortisone mouthwash three to four times a day and the results were evaluated after treatment for two weeks. The results are shown in **Table 9**.

Table 9

Clinical results of treatment of patients with hydrocortisone mouthwash.

Disease	Number of patients				
	Total	Worse	No Change	Improved	Relapsed*
Lichen Planus	17	1	2	14	1
Recurrent oral ulceration	6	0	0	6	1
Miscellaneous autoimmune disease	8	0	2	6	1

*Relapse, of those which showed improvement, within 6 months after end of treatment.

Quantitative analysis

The quantitative determinations of the individual drugs were performed on a reversed-phase high-performance liquid chromatographic (HPLC) component system consisting of a Milton Roy ConstaMetric 3200 solvent delivery system, a Rheodyne 7125 injector, a Spectro Monitor 3200 uv/vis variable wavelength detector and a LiChrosorb®RP-18 5µ (125 x 4mm) column. For other conditions, see **Table 10.** The quantitative determination of econazole was done spectrophotometrically (Perkin-Elmer 550SE uv/vis spectrophotometer) at wavelength 225nm. Solvent ratios indicated refer to parts by volume.

Table 10

Conditions of quantitative drug determination by HPLC.

Drug	Mobile phase	Flow rate (ml/min)	Wave length (nm)	Retention time (min)
Acetazolamide	Acetonitrile, acetic acid, water (10:2:88) containing 0.015% 1-octanesulfonate	1.5	263	4.0
Alprazolam	Methanol, water (70:30)	1.5	254	2.8
Butylated hydroxyanisole	Methanol, water (70:30)	1.5	285	3.6
Camphor	Methanol, water (70:30)	1.5	200	3.2
Chlorbutol	Acetonitrile, water (60:40)	1.5	205	2.0
Dexamethasone	Acetonitrile, tetrahydrofuran, water (30:5:65)	1.5	254	4.0
Diazepam	Methanol, water (75:25)	1.5	226	4.0
Ethoxyzolamide	Acetonitrile, water (35:65) containing 0.1% 1-hexanesulfonate	1.0	254	3.2
Hydrocortisone	Acetonitrile, tetrahydrofuran, water (30:1:69)	1.5	254	2.6
Methylparaben	Acetonitrile, water (36:64)	1.5	260	4.4
Methylyellow	Acetonitrile, water (78:22)	1.5	205	5.2

Table 10 -- continued

Drug	Mobile phase	Flow rate (ml/min)	Wave length (nm)	Retention time (min)
Miconazole	Methanol, 0.01M aqueous potassium phosphate solution (pH=4.5) (90:10)	1.5	272	2.6
Oxazepam	Methanol, tetrahydrofuran, water (55:2:43)	1.5	226	2.8
Pentachlorophenol	Acetonitrile, tetrahydrofuran, water (78:3:19)	1.5	248	2.4
Prednisolone	Acetonitrile, acetic acid, water (17:0.5:82.5)	1.5	242	4.0
Propylparaben	Acetonitrile, water (40:60)	1.5	260	5.2
Salicylic acid	Methanol, acetic acid, water (35:1:64)	1.5	300	4.8
Sulfamethoxazole	Acetonitrile, acetic acid, water (30:1:69)	1.5	253	2.4
Temazepam	Methanol, water (70:30)	1.5	275	2.8
Triamcinolone acetonide	Acetonitrile, water (42:58)	1.5	254	2.8
Trimetoprim	Methanol, acetic acid, water (39:1:60) containing 0.005M 1-pentasulfonate	1.5	287	2.4
Vanillin	Methanol, water (70:30)	1.5	275	2.4

Example 13

To aqueous solutions containing 20% (w/v) 2-hydroxypropyl-β- cyclodextrin (HPβCD) of molar substitution (MS) = 0.6 were added 0.25% (w/v) polyvinylpyrrolidone (PVP), 0.25% (w/v) sodium carboxymethylcellulose (CMC) or 0.25% (w/v) hydroxypropyl methylcellulose (HPMC). The resultant solutions were heated in sealed containers to 120°C and maintained at that temperature for 30 minutes, then were lyophilized. The solids thus obtained were ground with a mortar and pestle.

The solid cyclodextrin/polymer products were reconstituted with water to afford solutions containing 9.88%

(w/v) HPβCD and 0.12% (w/v) PVP, 0.12% (w/v) or CMC 0.12% (w/v) HPMC. The solubilities (S) of three drugs in these solutions and in an aqueous solution containing 10% (w/v) HPβCD without added polymer were then determined as follows:

An excess amount of each drug was added to each of the four cyclodextrin solutions and the solutions were sonicated in an ultrasonic bath for 3 hours, then allowed to equilibrate for 60 hours at room temperature (23°C). After equilibration, aliquots were filtered through 0.45mm membrane filters, diluted with a mixture of methanol and water and analyzed by an HPLC method. The results are set forth in **Table 11** below, where S_1 is the solubility in aqueous solution containing 10% (w/v) HPβCD; S_2 is the solubility in aqueous solution containing 9.88% (w/v) HPβCD and 0.12% (w/v) PVP; S_3 is the solubility in aqueous solution containing 9.88% (w/v) HPβCD and 0.12% (w/v) CMC; and S_4 is the solubility in aqueous solution containing 9.88% (w/v) HPβCD and 0.12% (w/v) HPMC. The results show that a solid polymer/cyclodextrin product can be prepared which has enhanced complexing abilities, and that the drug itself need not be heated to achieve enhancement. Nevertheless, it is expected that a greater increase in solubility would be observed at higher polymer concentrations [e.g. 0.25% (w/v)], and/or if the solutions were heated after addition of the drug. However, by separate preparation of the cyclodextrin/polymer complexing agent as illustrated here, one can readily avoid heating drugs which are unstable at elevated temperature.

Table 11

The effect of previously prepared solid HPβCD-polymer complexing agent mixture on the solubility of drugs. Solution S_1 contained 10% (w/v) HPβCD. Solutions S_2, S_3 and S_4 contained 9.88% (w/v) HPβCD and 0.12% (w/v) of the polymer.

Drug	S_1(mg/ml)	S_2(mg/ml)	S_3(mg/ml	S_4(mg/ml)
Carbamazepine	7.00	9.80	6.66	9.53
Econazole	4.86	5.57	5.20	6.32
Hydrocortisone	12.88	16.47	14.52	16.05

Example 14

Solubilities (S) of various compounds were determined in eight different solvents, i.e. a) water (S_1), b) aqueous 0.25% (w/v) sodium carboxymethylcellulose (CMC) solution (S_2), c) aqueous 0.25% (w/v) polyvinylpyrrolidone (PVP) solution (S_3), d) aqueous 0.25% (w/v) hydroxypropyl methylcellulose (HPMC) solution (S_4), e)

aqueous solution of 10% (w/v) 2-hydroxypropyl-β-cyclodextrin (HPβCD) of molar substitution (MS) = 0.6 (S_6), f) aqueous solutions containing both 0.25% (w/v) CMC and 10% (w/v) HPβCD MS = 0.6 (S_6), g) aqueous solutions containing both 0.25% (w/v) PVP and 10% (w/v) HPβCD MS = 0.6 (S_7), and h) aqueous solutions containing both 0.25% (w/v) HPMC and 10% (w/v) HPβCD MS = 0.6 (S_8). An excess amount of the compound to be tested was added to each solvent and the suspensions which formed were heated in sealed containers to 120°C. The solubility of salicylic acid was determined in acidic (HCl) solution. The suspensions were kept at this temperature for 20 minutes and then allowed to equilibrate for 3 days at room temperature (approximately 23°C). After equilibration, aliquots were filtered through 0.45 µm membrane filters, diluted with a mixture of methanol and water (7:3) and analyzed by a high pressure liquid chromatographic (HPLC) method. The results in **Table 12** show that the solubilizing effect of HPβCD was increased by 2 to 134% (solubility ratio of 1.02 to 2.34) when 0.25% polymer (CMC, PVP or HPMC) was present in the solution.

Table 12

The effect of polymers on the solubilization of various compounds in aqueous HPβCD solutions. The solubility ratios (the solubility in HPβCD solution containing the polymer divided by the solubility in HPβCD solution containing no polymer) are shown in parentheses.

Compound	S_1 (mg/ml)	S_2 (mg/ml)	S_3 (mg/ml)	S_4 (mg/ml)	S_5 (mg/ml)	S_6 (mg/ml)	S_7 (mg/ml)	S_8 (mg/ml)
Butylated hydroxyanisole	0.40	0.40	1.24	0.28	13.9	14.3 (1.03)	15.8 (1.14)	15.5 (1.12)
Camphor	1.84	2.01	2.20	1.92	12.7	13.8 (1.09)	13.7 (1.08)	13.3 (1.05)
Chlorbutol	8.11	8.41	8.41	8.15	28.6	29.3 (1.02)	-	29.9 (1.05)
Cholecalciferol	NO	NO	NO	NO	0.61	0.72 (1.18)	0.76 (1.25)	0.69 (1.14)
Methylparaben	3.16	3.16	3.40	3.16	8.46	-	10.5 (1.24)	11.4 (1.35)
Methylyellow	6.4×10^{-4}	8.5×10^{-4}	8.5×10^{-4}	7.5×10^{-4}	0.23	0.24 (1.04)	0.24 (1.04)	0.25 (1.09)
Pentachlorophenol	0.02	0.06	0.03	0.03	0.61	0.99 (1.62)	1.43 (2.34)	-

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Table 12 – continued

Compound	S_1 (mg/ml)	S_2 (mg/ml)	S_3 (mg/ml)	S_4 (mg/ml)	S_5 (mg/ml)	S_6 (mg/ml)	S_7 (mg/ml)	S_8 (mg/ml)
Propylparaben	0.19	0.33	0.29	0.29	8.28	8.90 (1.07)	9.00 (1.09)	8.85 (1.07)
Salicylic acid	-	-	-	-	3.71	4.23 (1.14)	4.07 (1.10)	3.92 (1.06)
Vanillin	13.9	13.7	11.5	17.1	25.0	27.3 (1.09)	-	26.5 (1.06)

-: Not tested.

NO: No solubility could be observed, the solubility was below the detection limits.

Example 15

The effect of polyvinylpyrrolidone (PVP) on transdermal delivery of hydrocortisone from aqueous 2-hydroxypropyl-β-cyclodextrin of molar substitution 0.6 (HPβCD MS 0.6) was investigated in vitro. Female hairless mice were sacrificed by cervical dislocation. The whole dorsal skin was removed and placed carefully in a Franz

diffusion cell containing 10 ml aqueous 5% (w/v) HPβCD MS 0.6 as the receptor phase. The donor phase consisted of a saturated hydrocortisone solution in (a) aqueous 8% (w/v) HPβCD MS 0.6 solution and (b) aqueous solution containing both 6% (w/v) HPβCD MS 0.6 and 0.25% (w/v) PVP, prepared as described in **Example 1.** [The amounts of cyclodextrin and polymer were selected such that solutions (a) and (b) achieved equivalent solubilizing of the drug.]. 2 Ml of the donor phase was applied to the skin surface (area 3.1 cm^2). The diffusion cells were kept at constant temperature circulating 37°C water from a constant temperature water bath and samples (500 µm) were removed at various time intervals, up to three days, from the donor phase and analyzed by HPLC. The results in **Table 13** clearly show that transdermal delivery of hydrocortisone was over two times faster from the PVP-containing sample.

Table 13

The concentration of a saturated solution (C) and the flux (F) of hydrocortisone through hairless mouse skin from HPβCS MS 0.6 containing vehicles. Each experiment was repeated 4 times and the results are the mean ± standard deviation.

Vehicle composition	C (mg/ml)	F (µm/cm^2/h)
Aqueous 8% (w/v) HPβCD MS 0.6 solution	10.9	0.075±0.023
Aqueous solution containing both 6% (w/v) HPβCD MS 0.6 and 0.25% (w/v) PVP	10.6	0.158±0.035

Example 16

Solubilities (S) of hydrocortisone in aqueous solutions containing four different cyclodextrins (CDs), i.e. hydroxyethyl-β-cyclodextrin (HEβCD) with molar substitution (MS) 0.6, methyl-β-cyclodextrin (MβCD) with degree of substitution 1.8, monosubstituted glucosyl-α-cyclodextrin (Glucosyl-αCD), monosubstituted glucosyl-β-cyclodextrin (Glucosyl-βCD), monosubstituted maltosyl-α-cyclodextrin (Maltosyl-αCD), or monosubstituted maltosyl-β- cyclodextrin (Maltosyl-βCD), with and without 0.25% (w/v) polymer, i.e. sodium carboxymethylcellulose (CMC), polyvinylyrrolidone (PVP) or hydroxypropyl methylcellulose (HMC), were determined as in **Example 1.** The results in **Table 14** show that the polymers increased the solubilizing effect of the CD derivatives by 8 to 100% (S_{cp}/S_{∞} = 1.08 to 2.00) when 0.25% polymer was present in the solution.

Table 14

The effect of polymers on the solubilization of hydrocortisone in aqueous CD solutions.

Cyclodextrin	Polymer	S_{co} [a] (mg/ml)	S_{cp} [b] (mg/ml)	S_{cp}/S_{co} [c]
HEβCD	CMC	17.5	26.8	1.53
MβCD	CMC	18.6	20.1	1.08
MβCD	PVP	18.6	20.2	1.09
MβCD	HMC	18.6	21.8	1.17
Glucosyl-αCD	CMC	2.7	5.4	2.00
Glucosyl-αCD	PVP	2.7	3.6	1.33
Glucosyl-αCD	HMC	2.7	5.4	2.00
Glucosyl-βCD	CMC	17.0	20.2	1.19
Glucosyl-βCD	PVP	17.0	22.2	1.31
Glucosyl-βCD	CMC	4.1	6.1	1.49
Maltosyl-αCD	CMC	10.4	18.3	1.76
Maltosyl-βCD	CMC	10.4	19.5	1.88
Maltosyl-βCD	PVP	10.4	17.9	1.72
Maltosyl-βCD	HMC			

[a] = Solubility in aqueous 10% (w/v) CD solution.
[b] = Solubility in aqueous solution containing both 0.25% (w/v) of the given polymer and 10% (w/v) CD.
[c] = The solubility ratio.

Example 17

The effect of polyvinylpyrrolidone (PVP) on the enthalpy (ΔH) and the entropy (ΔS) of the stability constant (K_c) of the drug-cyclodextrin complex was determined. The phase-solubility diagrams of hydrocortisone, 17β-estradiol and acetazolamide in aqueous 2-hydroxypropyl-β-cyclodextrin (HPβCD) of molar substitution (MS) 0.6, or aqueous 2-hydroxypropyl-α-cyclodextrin (HPαCD) MS 0.6 solutions, containing from 0 to 0.5% (w/v) PVP, were determined and the stability constant (K_c) was calculated for the complex from the slope (see **Example 4**).

An excess amount of the drug was added to water containing 0, 0.1, 0.25 or 0.5% (w/v) PVP and various amounts of HPβCD or HPαCD. The suspensions which formed were heated in sealed containers to 120°C and kept at that temperature for 22 minutes. After equilibration for at least seven days at 6, 20, 30, 40 and 50°C, aliquots of the suspensions were removed from the containers and each aliquot was filtered through a 0.45 μm membrane filter and analyzed by HPLC. K_c was calculated at each temperature and ΔH and ΔS were calculated as described in A. Martin, J. Swarbrick and A. Cammarata: *Physical Pharmacy: The Physical Chemical Principles in the Pharmaceutical Sciences*, Third Edition, Lea & Febiger, Philadelphia, 1983, Chapter 13, pp. 314-348.

The results are shown in **Tables 15-18** below.

Table 15

The effect of PVP on ΔH and ΔS for the stability constant (K_c) of the acetazolamide-HPβCD MS 0.6 complex.

PVP concentration (% w/v)	ΔH (kJ mol^{-1})	ΔS (J $mol^{-1}K^{-1}$)
0.00	-18.4	-26.0
0.10	-25.8	-49.6
0.25	-24.8	-46.2
0.50	-25.8	-49.8

Table 16

The effect of PVP on ΔH and ΔS for the stability constant (K_c) of the hydrocortisone-HPαCD MS 0.6 complex.

PVP concentration (% w/v)	ΔH (kJ mol^{-1})	ΔS (J $mol^{-1}K^{-1}$)
0.00	-32.1	-70.2
0.10	-39.3	-94.5
0.25	-48.4	-124.2
0.50	-35.7	-81.9

Table 17

The effect of PVP on ΔH and ΔS for the stability constant (K_c) of the hydrocortisone-HPβCD MS 0.6 complex.

PVP concentration (% w/v)	ΔH (kJ mol^{-1})	ΔS (J $mol^{-1}K^{-1}$)
0.00	-20.4	-6.2
0.10	-41.0	-68.6
0.25	-36.5	-56.4
0.50	-38.8	-64.9

Table 18

The effect of PVP on ΔH and ΔS for the stability constant (K_c) of the 17β-estradiol-HPβCD MS 0.6 complex.

PVP concentration (% w/v)	ΔH (kJ mol^{-1})	ΔS (J $mol^{-1}K^{-1}$)
0.00	-71.1	-151
0.10	-75.3	-166
0.25	-89.5	-213
0.50	-81.2	-185

It has been shown that ΔH and ΔS generally become more negative as the stability constant for molecular complexation increases (A. Martin, J. Swarbrick and A. Cammarata: *Physical Pharmacy: The Physical Chemical Principles in the Pharmaceutical Sciences,* Third Edition, Lea & Febiger, Philadelphia, 1983, Chapter 13, pp. 314-348). As the binding between the drug and the cyclodextrin becomes stronger, ΔH would be expected to have a larger negative value. Apparently, PVP increases the structural restraint of the complex in the aqueous solution, leading to a larger negative ΔS value. These thermodynamic changes indicate that the water-soluble PVP polymer participates directly in the complex formation.

While the invention has been described in terms of various preferred embodiments, the skilled artisan will appreciate that various modifications, substitutions, omissions and changes may be made without departing from the spirit thereof. Accordingly, it is intended that the scope of the present invention be limited solely by the scope of the following claims, including equivalents thereof.

Claims

1. A method for enhancing the complexation of cyclodextrin with a lipophilic and/or water-labile drug, said method comprising combining from about 0.1 to about 70% (weight/volume) of cyclodextrin and from about 0.001 to about 5% (weight/volume) of a pharmaceutically acceptable, pharmacologically inactive, water-soluble polymer in an aqueous medium, the polymer and cyclodextrin being dissolved in the aqueous medium before the drug is added, the aqueous medium which comprises the polymer and cyclodextrin being maintained at from about 30 to about 150°C for a period of from about 0.1 to about 100 hours before, during and/or after the drug is added, optionally followed by removal of water.

2. A method for enhancing the complexation of cyclodextrin with a lipophilic and/or water-labile cosmetic additive, food additive or agrochemical, said method comprising combining from about 0.1 to about 70% (weight/volume) of cyclodextrin and from about 0.001 to about 5% (weight/volume) of a water-soluble polymer acceptable for use in cosmetics, foods or agricultural compositions, in an aqueous medium, the polymer and cyclodextrin being dissolved in the aqueous medium before the cosmetic additive, food additive or agrochemical is added, the aqueous medium which comprises the polymer and cyclodextrin being maintained at from about 30 to about 150°C for a period of from about 0.1 to about 100 hours before, during and/or after the cosmetic additive, food additive or agrochemical is added, optionally followed by removal of water.

3. A method for solubilizing and/or stabilizing a lipophilic and/or water-labile drug in an aqueous medium, said method comprising complexing said drug in an aqueous medium comprising from about 0.1 to about 70% (weight/volume) of cyclodextrin and from about 0.001 to about 5% (weight/volume) of a pharmaceutically acceptable, pharmacologically inactive, water-soluble polymer, the polymer and cyclodextrin being dissolved in the aqueous medium before the drug is added, the aqueous medium which comprises the polymer and cyclodextrin being maintained at from about 30 to about 150°C for a period of from about 0.1 to about 100 hours before, during and/or after the drug is added.

4. A method for solubilizing and/or stabilizing a lipophilic and/or water-labile cosmetic additive, food additive or agrochemical in an aqueous medium, said method comprising complexing said cosmetic additive, food additive or agrochemical in an aqueous medium comprising from about 0.1 to about 70% (weight/volume) of cyclodextrin and from about 0.001 to about 5% (weight/volume) of a water-soluble polymer acceptable for use in cosmetics, foods or agricultural compositions, the polymer and cyclodextrin being dissolved in the aqueous medium before the cosmetic additive, food additive or agrochemical is added, the aqueous medium which comprises the polymer and cyclodextrin being maintained at from about 30 to about 150°C for a period of from about 0.1 to about 100 hours before, during and/or after the drug is added.

5. A co-complex of a lipophilic and/or water-labile drug, cosmetic additive, food additive or agrochemical with a cyclodextrin and a pharmaceutically acceptable, pharmacologically inactive, water-soluble polymer, the ratio by weight of cyclodextrin to polymer being from about 4:1 to about 50,000:1, preferably from about 100:1 to about 10,000:1.

6. A pharmaceutical composition comprising:
   (a) a drug complex prepared by complexing a lipophilic and/or water-labile drug with cyclodextrin in an aqueous medium comprising from about 0.1 to about 70% (weight/volume) of cyclodextrin and from about 0.001 to about 5% (weight/volume) of a pharmaceutically acceptable, pharmacologically inactive, water-soluble polymer, the polymer and cyclodextrin being dissolved in the aqueous medium before the drug is added, the aqueous medium which comprises the polymer and cyclodextrin being maintained at from about 30 to about 150°C for a period of from about 0.1 to about 100 hours before, during and/or after the drug is added, optionally followed by removal of water; and
   (b) a non-toxic, pharmaceutically acceptable carrier therefor.

7. A food or cosmetic composition comprising:
   (a) a complex of a food additive or cosmetic additive prepared by complexing a lipophilic and/or water-labile cosmetic additive or food additive with cyclodextrin in an aqueous medium comprising from about 0.1 to about 70% (weight/volume) of cyclodextrin and from about 0.001 to about 5% (weight/volume) of a water-soluble polymer acceptable for use in cosmetics or foods, the polymer and cyclodextrin being dissolved in the aqueous medium before the cosmetic additive or food additive is added, the aqueous medium which comprises the polymer and cyclodextrin being maintained at from about 30 to about

150°C for a period of from about 0.1 to about 100 hours before, during and/or after the cosmetic additive or food additive is added, optionally followed by removal of water; and
(b) a non-toxic carrier acceptable for use in cosmetics or foods.

8. An agricultural composition comprising:
(a) an agrochemical complex prepared by complexing a lipophilic and/or water-labile agrochemical with cyclodextrin in an aqueous medium comprising from about 0.1 to about 70% (weight/volume) of cyclodextrin and from about 0.001 to 5% (weight/volume) of an agriculturally acceptable water-soluble polymer, the polymer and cyclodextrin being dissolved in the aqueous medium before the agrochemical is added, the aqueous medium which comprises the polymer and cyclodextrin being maintained at from about 30 to about 150°C for a period of from about 0.1 to about 100 hours before, during and/or after the agrochemical is added, optionally followed by removal of water; and
(b) a non-toxic, agriculturally acceptable carrier therefor.

9. A composition comprising:
(a) a co-complex of a lipophilic and/or water-labile drug, cosmetic additive, food additive or agrochemical with a cyclodextrin and a pharmaceutically acceptable, pharmacologically inactive, water-soluble polymer, the ratio by weight of cyclodextrin to polymer being from about 4:1 to about 50,000:1, preferably from about 100:1 to 10,000:1; and
(b) a non-toxic, pharmaceutically acceptable carrier therefor.

10. A complexing agent for use in solubilizing and/or stabilizing a lipophilic and/or water-labile drug, cosmetic additive, food additive or agrochemical, said complexing agent comprising a cyclodextrin and a pharmaceutically acceptable, pharmacologically inactive, water-soluble polymer, the ratio by weight of cyclodextrin to polymer being from about 4:1 to about 50,000:1, preferably from about 100:1 to 10,000:1, said complexing agent being formed by heating the cyclodextrin and polymer in an aqueous medium at from about 30 to about 150°C for a period of from about 0.1 to about 100 hours.

11. A method according to any one of Claims 1 to 4 or a composition according to any one of Claims 6 to 9, wherein the amount of water-soluble polymer is from about 0.01 to about 0.5% (weight/volume).

12. A method, co-complex, composition or complexing agent according to any one of the preceding claims, wherein the cyclodextrin comprises at least one member selected from the group consisting of hydroxypropyl, hydroxyethyl, dihydroxypropyl, glucosyl and maltosyl derivatives of α,β-and γ-cyclodextrin, especially when the cyclodextrin has a molar degree of substitution of from about 0.05 to about 10.

13. A method, co-complex, composition or complexing agent according to any one of the preceding claims, wherein the water-soluble polymer is a cellulose derivative, a natural polysaccharide or polypeptide, or a synthetic polymer which is a polyvinyl polymer or a copolymer of acrylic acid.

14. A method, co-complex, composition or complexing agent according to Claim 13, wherein the cellulose derivative is methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl methylcellulose, hydroxypropyl ethylcellulose, hydroxyethyl ethyl cellulose or sodium carboxymethylcellulose; wherein the polysaccharide is inulin, pectin, sodium, alginate or agar; wherein the polypeptide is casein or gelatin; wherein the polyvinyl polymer is polyvinyl alcohol, polyvinylpyrrolidone or polystyrene sulfonate; or wherein the copolymer of acrylic acid is carbomer.

15. A method, co-complex, composition or complexing agent according to Claim 13, wherein the water-soluble polymer is hydroxypropyl methylcellulose, sodium carboxymethylcellulose or polyvinylpyrrolidone.

16. A method according to Claim 1 or 3, a co-complex according to Claim 5 or a composition according to Claim 6 or 9, wherein the drug is a carbonic anhydrase inhibitor, β-adrenergic blocking agent, steroid, sedative, tranquilizer, anticonvulsant, antidepressant, antipsychotic, hypnotic, muscle relaxant, antispasmodic, anticoagulant, cardiotonic, vasodilator, vasoconstrictor, platelet inhibitor, anti-arrhythmic, antihypertensive, antifungal, antiprotozoal, antibacterial, antibiotic, anti-infective, antiviral, anthelmintic, antineoplastic, vitamin, emetic, antiemetic, diuretic, non-steroidal analgesic or anti-inflammatory agent, anesthetic, hypoglycemic, radiodiagnostic, antihistaminic, serotonin antagonist, H2-antagonist, narcotic antagonist, narcotic agonist, mixed narcotic agonist-antagonist, pharmacologically active protein, dopaminergic/anti-Parkinsonism agent or agent for treating Alzheimer's disease.

17. A method, co-complex or composition according to Claim 16, wherein the steroid is an androgen, estrogen, progestin, diuretic, anabolic agent, anesthetic or glucocorticoid.

18. A method, co-complex or composition according to Claim 16, wherein the drug is acetazolamide, chlorzolamide, ethoxzolamide, methazolamide, timolol, atenolol, carbamazepine, phenytoin, ketoconazole, itraconazole, metronidazole benzoate, flubendazole, co-trimoxazole, miconazole, carmustine, chlorambucil, doxorubicin, lomustine, melphalan, methotrexate, dicumarol, nitroglycerin, flunarizine, alprostadil, prostacyclin, digitoxin, digoxin, aspirin, apomorphine, famotidine, furosemide, flubiprofen, ibuprofen, indomethacin, piroxicam, lidocaine, sulindac, pentobarbital, phenobarbital, secobarbital, chlordiazepoxide, diazepam, medazepam, oxazepam, lorazepam, flunitrazepam, estazolam, flurazepam, loprazolam, lormetazepam, nitrazepam, quazepam, temazepam or triazolam.

19. A method, co-complex or composition according to Claim 17, wherein the drug is hydrocortisone, dexamethasone, prednisolone, 17β-estradiol, 17α-ethinylestradiol, ethinylestradiol 3-methyl ether, estriol, norethindrone, norethindrone acetate, norgestrel, ethisterone, methoxyprogesterone acetate, progesterone, 17-methyltestosterone, triamcinolone, triamcinolone acetonide, testosterone, spironolactone or alfaxalone.

20. A method according to Claim 1 or 3, a co-complex according to Claim 5 or a composition according to Claim 6 or 9, wherein the drug is the reduced, biooxidizable, blood-brain barrier penetrating, lipoidal dihydropyridine form of a dihydropyridine ⇄ pyridinium salt redox system for brain-targeted drug delivery, preferably wherein the dihydropyridine form is a compound of the formula

[D-DHC]

wherein [D] is a centrally acting drug species and [DHC] is the reduced, biooxidizable, blood-brain barrier penetrating, lipoidal form of a dihydropyridine ⇄ pyridinium salt redox carrier, especially when the centrally acting drug species is dopamine, testosterone, phenytoin, GABA, valproic acid, tyrosine, methicillin, oxacillin, benzylpenicillin, cloxacillin, dicloxacillin, desipramine, acyclovir, trifluorothymidine, zidovudine, hydroxy-CCNU, chlorambucil, tryptamine, dexamethasone, hydrocortisone, ethinyl estradiol, norethindrone, estradiol, ethisterone, norgestrel, estrone, estradiol 3-methyl ether, estradiol benzoate, norethynodrel, mestranol, indomethacin, naproxen, FENU, HENU or 5-FU.

21. A method, co-complex or composition according to any one of Claims 16-20, wherein the cyclodextrin is as defined in Claim 12 and the polymer is as defined in any one of Claims 13 to 15, especially when the cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin, the polymer is hydroxypropyl methylcellulose, sodium carboxymethylcellulose or polyvinylpyrrolidone and the drug is a carbonic anhydrase inhibitor or a steroid.

22. A composition according to Claim 6, 9 or 11, wherein all ingredients are ophthalmically acceptable, and wherein the drug is a carbonic anhydrase inhibitor or a steroid, the polymer is hydroxypropyl methylcellulose, sodium carboxymethylcellulose or polyvinylpyrrolidone and the cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

23. A composition according to Claim 6, 9 or 11, wherein all ingredients are acceptable for use in a mouthwash, and wherein the drug is a steroid, the polymer is hydroxypropyl methylcellulose, sodium carboxymethylcellulose or polyvinylpyrrolidone and the cyclodextrin is hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

24. A method according to Claim 2 or 4, a co-complex according to Claim 5 or a composition according to Claim 7, 8 or 9, wherein the food or cosmetic additive is a flavoring agent or fragrance, preservative, antioxidant, sweetening agent, coloring agent or vitamin, or wherein the agrochemical is a fungicide, herbicide or plant growth regulator, or an insecticide, nematocide or other pesticide.

Fig. 1

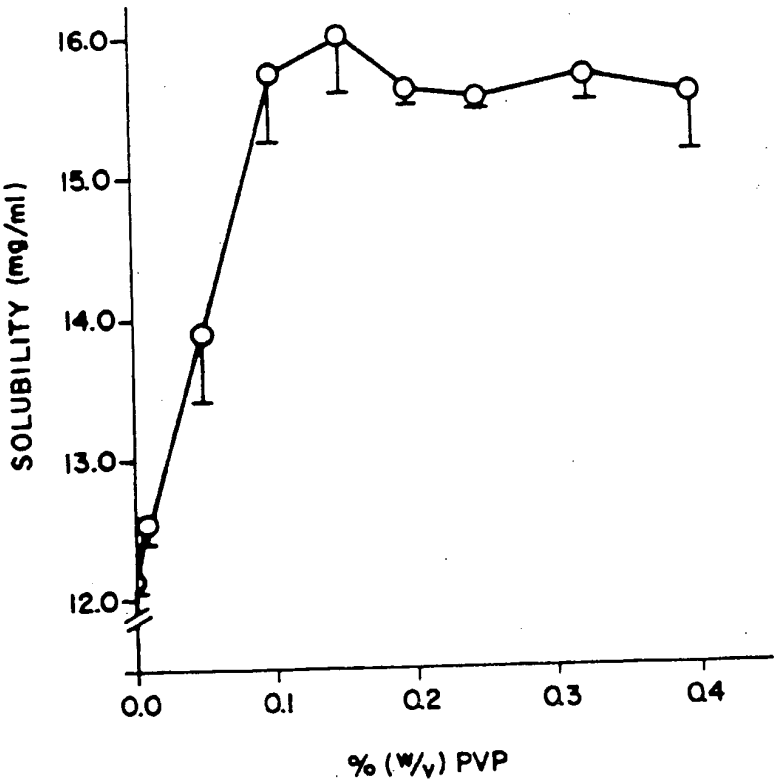


Fig. 2

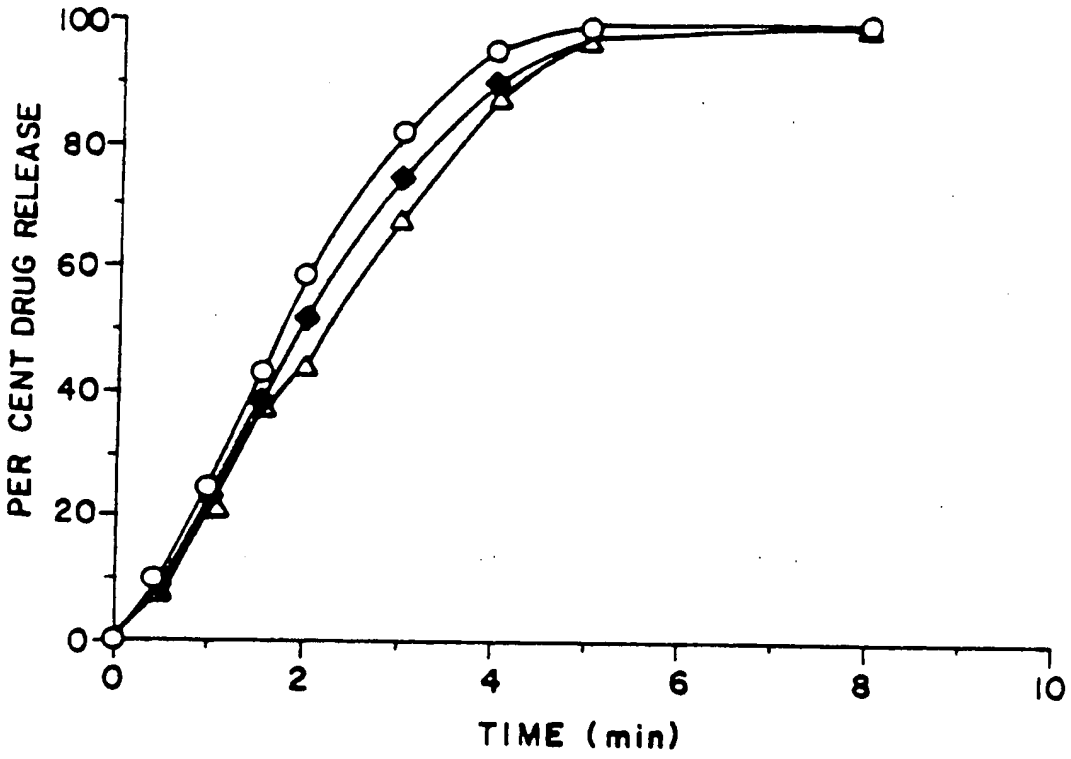
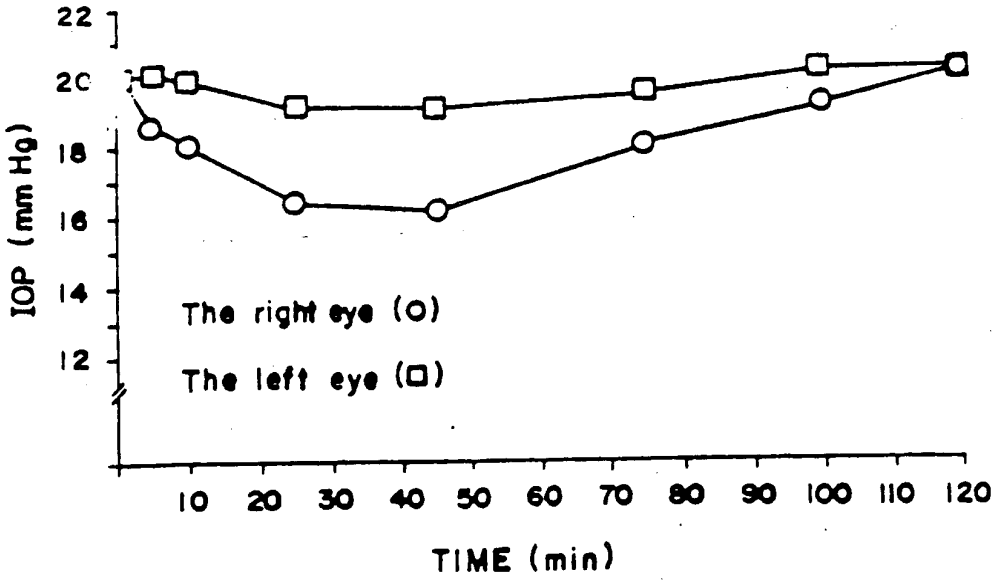


Fig. 3


22
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IOP (mm Hg)
The right eye (O)
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TIME (min)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 93 30 5280

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 5)
X,Y	EP-A-0 213 514 (TAKEDA CHEMICAL INDUSTRIES, LTD) 11 March 1987 * page 2, line 20 - page 33, line 22; examples * ---	1-24	A61K47/48
D,Y	EP-A-0 149 197 (JANSSEN PHARMACEUTICA N.V.) 24 July 1985 * page 5, line 23 - line 28; example 5 * * page 6, paragraph 3 * ---	1-24	
X,Y	STN FILE SUPPLIER & FILE MEDLINE AN=92324215 (KARLSRUHE) & EUR. J. DRUG METAB. PHARMACOKINET. no. 3, 1991, I. ORIENTI ET AL. 'CONTROLLED RELEASE OF HYDROCORTISONE ACETATE FROM DERMAL BASES. (SPEC. NO 3 466-72)' --- -/--	1-24	

TECHNICAL FIELDS SEARCHED (Int. Cl. 5)

A61K

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
THE HAGUE	20 SEPTEMBER 1993	BERTE M.J.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04E07)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number EP 93 30 5280

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. 5)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X,Y	CHEMICAL ABSTRACTS, vol. 107, no. 16, 1987, Columbus, Ohio, US; abstract no. 140916f, * abstract * & JP-A-62 114 909 (NIPPON EKISHO K. K.) 26 May 1987	1-24	
X	WO-A-9 209 307 (KABI PHARMACIA AB) 11 June 1992 * page 17; example II *	1-6,9-19	
X	DATABASE WPIL Week 9037, Derwent Publications Ltd., London, GB; AN 90-279330 & JP-A-2 196 863 (TAIYO CHEMICAL KK) 3 August 1990 * abstract *	1-24	TECHNICAL FIELDS SEARCHED (Int. Cl. 5)
Y	WO-A-9 104 026 (AUSTRALIAN COMMERCIAL RESEARCH & DEV. LTD.) 4 April 1991 * claims *	1-24	
A	EUR. J. PHARM. BIOPHARM. vol. 37, no. 1, March 1991, pages 30 - 33 T. LOFTSSON ET AL. 'THE EFFECTS OF CYCLODEXTRINS ON TRANSDERMAL DELIVERY OF DRUGS.' * summary *	1-24	
D,Y	EP-A-0 327 766 (UNIVERSITY OF FLORIDA) 16 August 1989 * claims * & US-A-5 024 998	1-24	

EPO FORM 1503 03.82 (P0E10)

EP 93 30 5280

-C-

INCOMPLETE SEARCH

Claims searched incompletely: 1-24

On ground of expressions or terms such as "lipophilic, water-labile drug, water-soluble polymer, food or cosmetic additive, agrochemical, fragance, herbicide" and many others, it is not possible to carry out a complete search on all or some of the claims, of the state of the art.
A search was conducted of the above expressions and terms in the light of the examples.
In view of the large number of compounds represented in claims 16,17,18,19,20,24 the search was limited to the general inventive idea and compounds mentioned in the examples and that for economic reasons.
(See Guidelines part B, chapter II.7, chapter III,3.7 of the EPC).